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CANNABIS USE AND THE DEVELOPMENT OF TOLERANCE: A SYSTEMATIC REVIEW OF HUMAN EVIDENCE

Running title: Tolerance to cannabis use

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HIGHLIGHTS

- Cannabis has less prominent effects in regular users compared to non-regular users
- The behavioral and physiological effects of cannabis lessen over repeated exposure
- The acute effects of cannabis are less prominent during Δ9-THC active maintenance
- Cognitive function is the domain showing the highest degree of tolerance

- The acute intoxicating, psychotomimetic and cardiac effects show partial tolerance

ABSTRACT

Previous studies have reported conflicting results in terms of acute effects of cannabis in man. Independently of other factors, such discrepancy may be attributable to the different cannabis use history of study volunteers. It is thought that regular cannabis users may develop tolerance to the effects of acute cannabis administration. Here we systematically review all studies examining the effects of single or repeated cannabinoid administration in man as a function of previous cannabis exposure. Research evidence tends to suggest that the acute effects of single cannabinoid administration are less prominent in regular cannabis users compared to non-regular users. Studies of repeated cannabinoid administration more consistently suggest less prominent effects upon repeated exposure. Cognitive function is the domain showing the highest degree of tolerance, with some evidence of complete absence of acute effect (full tolerance). The acute intoxicating, psychotomimetic, and cardiac effects are also blunted upon regular exposure, but to a lesser extent (partial tolerance). Limited research also suggests development of tolerance to other behavioral, physiological, and neural effects of cannabis.

Keywords: Cannabis; Delta-9-tetrahydrocannabinol; Tolerance; Health; Cannabinoid receptor type 1

1. INTRODUCTION

Cannabis is the most widely used illicit drug all over the world. Population data suggests that approximately 200 million people use cannabis (National Academies of Sciences, 2017) and an estimated 13 million individuals have a Cannabis Use Disorder (CUD, DSM-5, American Psychiatric Association, 2013) (Degenhardt et al., 2013). The prevalence of cannabis use is expected to increase following the current trend to decriminalize or legalize its use for therapeutic and recreational purposes (Hall and Lynskey, 2016; Hasin et al., 2017). However, the safety of recreational use of cannabis has been questioned by numerous epidemiological and clinical studies which have suggested an association between acute and chronic cannabis use on one hand, and development of a CUD as well as a number of adverse effects on physical and mental health, cognition, and psychomotor function on the other (Batalla et al., 2014; Bhattacharyya et al., 2012a; Blest-Hopley et al., 2018; Ford et al., 2017; Hall, 2015; Schoeler et al., 2016). Consistently, acute administration of delta-9-tetrahydrocannabinol (Δ9-THC), the main psychoactive ingredient of the *Cannabis sativa* plant, has been shown to induce physiological and psychiatric symptoms as well as neurocognitive and motor impairments (Batalla et al., 2014; Bhattacharyya et al., 2017; Bhattacharyya et al., 2015; Colizzi and Bhattacharyya, 2017; Curran et al., 2002; D'Souza et al., 2004; Ramaekers et al., 2006). Therefore, the effects of cannabis on cognition and health remain an important public health concern, especially in light of regulatory trends worldwide.

To date, most experimental studies investigating the acute effects of cannabis or Δ9-THC have been conducted in otherwise healthy cannabis users with a relatively low average frequency of lifetime cannabis use. However, using different methodologies, a number of studies have provided evidence that tolerance may develop to most of the subjective and behavioral effects of cannabis. In particular, studies conducted in the last decade have indicated that a single acute administration of Δ9-THC induce less pronounced subjective, cognitive, behavioral, electrophysiological, neurochemical, and neuroendocrine effects in frequent cannabis users compared to occasional users (Cortes-Briones et al., 2015; D'Souza et al., 2008a; D'Souza et al., 2012; D'Souza et al., 2009; D'Souza et al., 2008b; Ramaekers et al., 2009; Ranganathan et al., 2009; Schoeler and Bhattacharyya, 2013). Also, early studies have suggested that repeated cannabis administration reduces the subjective and physiological responses to re-challenge with cannabis (Haney et al., 1999; Kirk and de Wit, 1999; Nowlan and Cohen, 1977).

Development of tolerance might explain why some studies conducted only in frequent cannabis users failed to show a clear effect of acute cannabis administration on cognitive performance (Hart et al., 2010; Hart et al., 2001; Ramaekers et al., 2011). Nevertheless, other similar studies indicate that frequent cannabis users report impairments in a broad range of cognitive domains upon acute Δ9-THC administration (Metrik et al., 2012; van Wel et al., 2013). One potential explanation accounting for this discrepancy across studies could be that frequent cannabis users may not develop tolerance for every performance domain. Studies assessing a wider range of neuropsychological and physiological outcomes, only in frequent cannabis users (Hart et al., 2010) or in comparison to occasional users (Ramaekers et al., 2009), suggest the development of tolerance to the effects of Δ9-THC on certain cognitive indices but not on psychomotor function, subjective-effect ratings, and physiological measures. Therefore, the role of previous cannabis exposure as a predictor of blunted response to cannabis intoxication is still debated. Understanding this appears also to be relevant to public policy debates regarding reform of laws related to cannabis use. For instance, in light of the potential development of tolerance to the acute effects of cannabis among regular users, some concern has been raised about the imposition of criminal liability for drivers who test positive for Δ9-THC without additional demonstrable evidence of psychomotor impairment (Armentano, 2013).

The purpose of this review is to summarize all available data generated by studies that have investigated development of tolerance to the acute effects of cannabis and/ or Δ9-THC in man by carrying out a systematic literature search for all such data.

1.1. Objectives

Our main objective was to carry out a systematic review of all available literature concerning the development of tolerance to the effects of cannabis and Δ9-THC in humans. Our aim was twofold: 1) To review which domains show tolerance upon repeated cannabis administration; 2) To review the extent to which tolerance develops for these domains.

2. METHODS

2.1. Inclusion/exclusion criteria

In order to summarize previous literature investigating the development of tolerance to the effects of cannabis and Δ9-THC in man, inclusion criteria for studies were: (1) human studies, (2) studies investigating the impact of a single administration of Δ9-THC or cannabis in 2 or more populations with different levels of previous cannabis exposure (i.e. frequent users, occasional users, naïve individuals), (3) studies investigating the impact of a single administration of Δ9-THC or cannabis in a single population with variation in the extent of previous cannabis exposure (i.e. correlating the acute effect of Δ9-THC or cannabis on the outcome measure with the extent of previous cannabis exposure), or (4) studies investigating the impact of repeated administration of Δ9-THC or cannabis in population(s) of cannabis users (i.e. (re)assessing the outcome measure after every administration). In order to offer a comprehensive evaluation of the association between cannabis use and development of tolerance, a wide range of different outcome measures that have been reported in the literature were considered, including, but not limited to, questionnaire data, laboratory tests, performance, physiological and neurobiological measures. Exclusion criteria were (1) studies where the effects of Δ9-THC or cannabis were not investigated under experimental conditions, (2) studies in which groups were not differentiated in terms of previous cannabis exposure, (3) studies which primarily assessed the effects of psychoactive substances other than cannabis, and (4) studies which primarily/ exclusively assessed cannabinoid pharmacokinetics without investigating other outcomes of interest.

2.2. Search Strategy

A literature search was performed using electronic databases (MEDLINE, Web of Science and Scopus) for any published original English-language research, using a combination of search terms describing cannabis ("marijuana", "cannabis", "THC/ delta-9-tetrahydrocannabinol/ dronabinol"), its pattern of use ("heavy", "regular", "frequent", "light", "non-regular", "occasional"), the study design ("acute", "challenge", "administration"), and the outcome of interest ("tolerance", "sensitization"), with a first search done on December 21, 2017, and a final search done on June 18, 2018. Reference lists of eligible studies were also screened to identify additional relevant studies.

2.3. Risk of bias

Risk of bias and quality assessment of the methodologically heterogeneous group of studies reviewed here (Table 1) required a suitably inclusive and flexible approach. For this purpose, an adapted set of criteria suggested by the Agency for Healthcare Research and Quality (AHRQ) guidance (West et al., 2002), amended as appropriate for interventional studies in humans was used (Table 2). Risk of systematic bias across human studies was further identified by assessing all papers for possible confounding factors such as mental health comorbidity, tobacco, alcohol, and other substance use among study samples (Table 2).

2.4. Calculation of the degree of tolerance development

Whenever possible, development of tolerance was calculated in terms of percentage reduction. In light of methodological heterogeneity across studies (Table 1), a flexible approach was required to calculate this percentage according to the study design. In principle, the effect of cannabis during the "tolerance phase" (or in regular users as the "tolerant group") was subtracted from the effect of cannabis during the "non-tolerance phase" (or in non-regular users as the "non-tolerant group"), divided by the reference value (pre-drug value; non-regular users placebo value; "non-tolerance phase" placebo value), and multiplied by 100. Further information on how the percentage was calculated for each specific study is reported in the Supplementary Methods.

3. RESULTS

3.1. Evidence at a glance

A number of studies have assessed the effects of Δ9-THC administration on subjective experiences, task performance on various cognitive and motor tasks, and physiological measures in volunteers with a previous history of frequent (Hart et al., 2010; Hart et al., 2001; Metrik et al., 2012; Ramaekers et al., 2011; van Wel et al., 2013) *or* occasional (Curran et al., 2002; Ramaekers et al., 2006) cannabis exposure, and have reported conflicting results. Some studies tend to confirm that the impairing effects of Δ9-THC observed in occasional cannabis users (Curran et al., 2002; Ramaekers et al., 2006) are absent in frequent cannabis users (Hart et al., 2001; Ramaekers et al., 2011). In contrast, other evidence from similar studies suggests that frequent cannabis users are still sensitive to the detrimental effects of Δ9-THC (Metrik et al., 2012; van Wel et al., 2013) or develop selective tolerance, i.e., showing tolerance to the cognitive effects of Δ9-THC while still remaining sensitive to its subjective and physiological effects (Hart et al., 2010).

In total 1252 records were identified. All abstracts of the records were screened against the inclusion and exclusion criteria (Figure 1). A final list of 36 studies reporting on a total of 1047 study participants (male = 782, female = 225; not specified = 40; Table 1) were identified which specifically investigated in otherwise healthy cannabis users whether tolerance develops to the acute effects of cannabis. These studies have used different experimental designs and studied heterogeneous populations. Further information on methodological quality of studies is reported in Table 2. These studies investigated whether the acute effects of cannabis vary: (i) between groups with different levels of previous cannabis exposure; (ii) within a group of individuals with different levels of previous cannabis exposure; (iii) upon repeated exposure; and (iv) upon concomitant treatment ('maintenance') with Δ9-THC. For the purpose of this review, in order to have a consistent nomenclature across studies, groups of "frequent" or "heavy" cannabis users were subsumed under the "regular" cannabis user group (RU). Similarly, groups of "infrequent" or "occasional" cannabis users were considered as "non-regular" cannabis users (NRU; Table 2). In general, RU had: (i) a pattern of daily or weekly cannabis use; (ii) a history of recent cannabis use and/ or a urine drug screen (UDS) positive for cannabis at the time of the study; and (iii) a diagnosis of Cannabis Use Disorder and/ or a history of chronic exposure lifetime (often ≥ 100 times). Conversely, NRU had: (i) a pattern of weekly cannabis use or less; (ii) a negative history of recent cannabis use and/ or a urine drug screen (UDS) negative for cannabis at the time of the study; and (iii) a history of lifetime occasional or experimental exposure (often from < 5 to 100 times).

The most commonly investigated domains were subjective effects and intoxication, cognitive function, psychopathology, cardiac function, and pharmacokinetics. Other behavioral parameters less frequently studied involved food intake, social behavior, sleep quality, and driving skills. Finally, a number of studies investigated other physiological and neurophysiological parameters, including neurochemical, electrophysiological, and laboratory markers (Table 3).

3.2. Intoxication and other subjective effects

Intoxication and other subjective effects represent the outcome measure most commonly investigated in studies of tolerance to the effects of cannabinoids, with 22 studies conducted over the last 50 years. Single administration of marijuana cigarettes and/ or intravenous Δ9-THC didn't induce different levels of intoxication in regular users (RU) and non-regular users (NRU) in four studies (Bosker et al., 2012; D'Souza et al., 2012; D'Souza et al., 2008b; Lindgren et al., 1981) [N (M ± SD, range): RU = 11.7 ± 2.6, 9-14; NRU = 11 ± 1.7, 9-12]. Conversely, marijuana administration produced less pronounced and shorter intoxication in RU compared to NRU in 3 other studies conducted in larger samples (Lex et al., 1984; Ponto et al., 2004 (degree of tolerance observed: "High", 89.5%; Cohen's *d*: 0.98); Fabritius et al., 2013) [N (M ± SD, range): RU = 14.7 ± 7.4, 9-23; NRU = 19.7 ± 8.4, 10-25]. Studies of repeated Δ9-THC or cannabis administration have more consistently demonstrated the development of tolerance to its intoxicating effects. In 1975, the first study with this experimental design comparing intoxication between RU and NRU indicated a trend level decrease in subjective intoxication upon continued marijuana exposure only in RU (Babor et al., 1975). A similar study involving repeated administration of Δ9-THC and crude cannabis extract in RU indicated a significant decrease in self-reported intoxication and sedation over the study period, but no significant changes in other subjective reports such as "Good feelings" and "Withdrawal" (Jones et al., 1976 (degree of tolerance observed: "Sedation", 267.5%)). Other studies indicated that repeated Δ9-THC administration in RU result in a significant decrease in intoxication as well as other subjective effects (e.g. ratings of "Good drug effect" and "Stimulated") (Gorelick et al., 2013 (degree of tolerance observed: "Good drug effect", 633.3%; "High", 276.5%); Haney et al., 1999) including ratings of strength, liking, and willingness to take the dose again (Haney et al., 1999). Another study indicated that intoxication reduces upon repeated marijuana administration in cannabis users, showing partial recovery after 1 week of abstinence (Nowlan and Cohen, 1977), with intoxicating effects fading away more rapidly in RU with a heavier pattern of cannabis use compared to other groups with light to moderate cannabis use (Nowlan and Cohen, 1977). Interestingly, three studies found that 10-15 min of marijuana smoking was sufficient to detect tolerance to the intoxicating effects of Δ9-THC, with RU showing less intoxication than NRU (Ramaekers et al., 2009; Theunissen et al., 2012 (degree of tolerance observed: "High", 29.1%); Desrosiers et al., 2015). Similarly, 2-3 min of vaporized cannabis induced less intoxicating effects with increasing frequency of past cannabis use (Ramaekers et al., 2016). Finally, a study comparing different routes of administration indicated that oral cannabis elicit intoxicating and subjective effects only in NRU, whereas vaporization and smoking had similar effects in RU and NRU. Also, "Good drug effect" and "Stoned" effect were higher under vaporized cannabis compared to oral cannabis only in RU (Newmeyer et al., 2017a (degree of tolerance observed: "Good drug effect", 245.4%; "Stoned", 1166.7%)).

Meyer et al. reported a number of subjective experiences acutely induced by marijuana smoking, including changes in feeling, thinking, bodily sensation, perception, and general awareness. However, there was no difference between the responses of RU and NRU (Meyer et al., 1971). In other studies, RU didn't show any significant change in identical (Bedi et al., 2010) or comparable (Vandrey et al., 2013) subjective measures upon repeated

Δ9-THC administration. Kirk and De Wit found that NRU report greater sedative effects than RU at higher Δ9-THC doses, also reporting less stimulant and liking effects compared to a lower dose. Interestingly, the lower dose increased ratings of "Feel drug," and "High" only in RU (Kirk and de Wit, 1999). Another study indicated attenuated marijuana-induced subjective effects during active maintenance with Δ9-THC in RU (Hart et al., 2002).

3.3. Cognitive function

Sixteen studies were identified specifically investigating the development of tolerance to the cognitive effects experienced upon acute intoxication with cannabis. The first study was performed in 1971 by Meyer et al. who compared the effect of marijuana smoking on several cognitive domains in RU and NRU. Upon acute intoxication, only NRU showed impairment in sustained attention. In contrast, groups did not differ significantly in their psychomotor ability, time sense, distractibility, and hand-eye coordination, even though impairments in these cognitive domains were evident to a greater extent in NRU than RU (Meyer et al., 1971). A more recent study indicated that the detrimental effects of marijuana smoking on divided attention are specific to NRU (Theunissen et al., 2012 (degree of tolerance observed: "DAT hits", 9.8%)). Similar findings on attention were reported in another study which compared NRU and non-users (NU), wherein they reported that upon acute intoxication NRU were less impaired than NU while performing a divided attention task (Marks and MacAvoy, 1989).

A second study investigating psychomotor ability with the same task used by Meyer et al (Meyer et al., 1971), the Digit-Symbol Substitution Test (DSST), indicated a dose-dependent detrimental effect of Δ9-THC administration on this cognitive domain and confirmed that the decrease in performance doesn't differ between RU and NRU (Kirk and de Wit, 1999). However, in recent years Ramaekers et al. have indicated that Δ9-THC marijuana smoking impairs psychomotor ability, divided attention, and motor impulsivity in NRU, while impairing only motor impulsivity in RU at high Δ9-THC concentrations (Ramaekers et al., 2009), suggesting that RU develop tolerance also to the effect of Δ9-THC on psychomotor ability (Ramaekers et al., 2009). It is worth mentioning that this study used a different task, the Critical Tracking Test (CTT), which specifically assesses psychomotor coordination rather than a wider range of psychomotor functions at the same time as for the DSST (Jongen et al., 2015). Similar findings were reported in 2015 by Desrosiers et al. who showed that the Δ9-THC marijuana impairs CTT psychomotor ability and divided attention more prominently in NRU than RU, also increasing the number of tracking errors and false alarms as well as prolonging reaction times during divided attention only in NRU (Desrosiers et al., 2015). However, RU and NRU didn't differ in terms of working memory or risk-taking and impulsivity (Desrosiers et al., 2015). Another study by Ramaekers and colleagues confirmed that Δ9-THC-induced CTT psychomotor ability impairment decreases with increasing frequency of past cannabis use, while Δ9-THC effects on executive function, impulse control, and divided attention are not affected by previous cannabis use (Ramaekers et al., 2016). Interestingly, in 2002 Hart et al. showed that marijuana smoking doesn't markedly impair DSST psychomotor performance in RU during active maintenance with Δ9-THC. Also, while acutely intoxicated with marijuana, RU performed better during active maintenance at the higher Δ9-THC dose compared to the lower dose or placebo (Hart et al., 2002).

A study in 1974 investigated the effect of marijuana smoking on verbal learning, indicating that RU performed similarly on a paired associate task whether intoxicated or not, while NRU tended to have a worse performance under the effect of marijuana (Cohen and Rickles, 1974). Also, NRU tended to perform better than RU under placebo, but worse under the effect of marijuana (Cohen and Rickles, 1974 (degree of tolerance observed: "Learning", 82.1%)). In more recent years, a number of studies conducted by D'Souza and colleagues confirmed and extended these findings. In particular, intravenous administration of Δ9-THC appeared to impair immediate and delayed free recall at a verbal learning task more markedly (D'Souza et al., 2008b) or only (D'Souza et al., 2008a) in NRU compared to RU, despite worse baseline performance in RU compared to NRU (D'Souza et al., 2008b). Interestingly, during the delayed recall RU performed significantly better under Δ9-THC than placebo (D'Souza et al., 2008b). Also, detrimental effects of acute Δ9-THC challenge on spatial working memory were more prominent in NRU than RU (D'Souza et al., 2008a; D'Souza et al., 2009). However, these studies found that sustained attention performance during a Continuous Performance Task didn't differ between RU and NRU (D'Souza et al., 2008a; D'Souza et al., 2008b). Along with previous evidence of absent or less marked impairment in divided attention with increasing frequency of past cannabis use (Desrosiers et al., 2015; Marks and MacAvoy, 1989; Ramaekers et al., 2009; Theunissen et al., 2012), these studies suggest selective development of tolerance for the effects of cannabis on divided attention but not on sustained attention.

A single study specifically assessed the effect of intravenous administration of Δ9-THC on time perception, indicating that Δ9-THC transiently impairs time estimation and production (Sewell et al., 2013). However, RU experienced less temporal distortion from Δ9-THC than NRU (Sewell et al., 2013; degree of tolerance observed: "Time estimation", 11.2%; "Time production", 8.9%).

Studies of repeated Δ9-THC or cannabis administration have more consistently demonstrated the development of tolerance to its impairing effects on cognition. In 1976, an early study of repeated administration of Δ9-THC and cannabis crude extract in RU indicated that the ability to visually track a moving target and to perform cognitive and psychomotor tasks shows initial impairments and then returns to baseline or even better than pre-drug performance levels, despite continuous drug administration (Jones et al., 1976). Another study indicated relatively minor disruptive effects of repeated Δ9-THC administration in RU on a number of cognitive domains including learning, memory, vigilance, and psychomotor ability, despite 4 days of abstinence preceding the drug challenge (Haney et al., 1999) while a more recent study reported no significant effects of repeated dronabinol (synthetic form of Δ9-THC) administration on similar cognitive tasks in RU (Bedi et al., 2010).

3.4. Psychopathology

Tolerance to the psychopathological effects of cannabis has received relatively less attention compared to other outcome measures, with the majority of the studies conducted in recent years. In 2008 a study by D'Souza et al. indicated blunted perceptual alterations, psychotomimetic symptoms, and anxiety in RU compared to NRU following a single intravenous administration of Δ9-THC (D'Souza et al., 2008b). Using the same assessment instruments, similar findings indicating less pronounced perceptual alterations and psychotomimetic symptoms in RU compared to NRU (D'Souza et al., 2009) as well as in recent cannabis users compared to non-recent users (D'Souza et al., 2012) were reported by the same group in subsequent studies conducted in non-overlapping samples. Using a similar methodology, Barkus et al. replicated these findings in 2011, indicating that the higher the previous use of cannabis the lower is the induction of psychotomimetic symptoms following acute challenge with Δ9-THC (Barkus et al., 2011). Further evidence indicated less anxiety in RU than NRU following 10 min of marijuana smoking (Desrosiers et al., 2015). Other evidence indicated less intense (Fabritius et al., 2013) and shorter confusion (Lex et al., 1984; Fabritius et al., 2013) in RU compared to NRU following Δ9-THC marijuana smoking.

Only three studies of repeated Δ9-THC or cannabis administration were identified which specifically investigated the development of tolerance to the psychoactive effects of cannabis. These studies focused on mood changes and reported conflicting results. Meyer et al. in 1971 didn't find any difference in mood states between RU and NRU after marijuana smoking, apart from the "vigor" factor. In particular, under marijuana RU tended to become more vigorous while NRU less vigorous (Meyer et al., 1971). However, Jones et al in 1976 found that upon repeated administration of Δ9-THC and cannabis crude extract there is a progressive lessening of the intensity of the mood changes experienced while intoxicated (Jones et al., 1976 (degree of tolerance observed: "Anxiety", 80%). This finding was not confirmed by a study of repeated Δ9-THC administration conducted in 2010, indicating sustained self-reported positive mood effects of Δ9-THC, which do not decrease over time (Bedi et al., 2010).

3.5. Cardiac function

Cardiac parameters have been frequently investigated in studies of tolerance to the effects of cannabinoids. Meyer et al. indicated that about 1 hour after smoking marijuana RU had a lower pulse rate compared to NRU (Meyer et al., 1971). Four subsequent studies conducted in larger samples confirmed that after smoking marijuana tachycardia is lower or less prolonged in RU compared to NRU (Lex et al., 1984; Desrosiers et al., 2015; Ponto et al., 2004 (degree of tolerance observed: "Pulse rate", 13.2%; Cohen's *d*: 0.79); Ramaekers et al., 2009) [N (M ± SD, range): RU = 10.6 ± 3.1, 6-14; NRU = 12.6 ± 6.8, 6-24]. However, three other studies involving single or limited exposure to Δ9-THC or marijuana didn't replicate this finding (Kirk and de Wit, 1999; Lindgren et al., 1981; Renault et al., 1971) [N (M ± SD, range): RU = 8.7 ± 2.5, 6-11; NRU = 7.7 ± 3.2, 4-10]. Another study also indicated that oral cannabis-induced tachycardia occurs at higher Δ9-THC blood levels only in NRU (Newmeyer et al., 2017a). Three of these studies suggested no difference in the effects of cannabis on blood pressure between RU and NRU (Newmeyer et al., 2017a; Ponto et al., 2004; Ramaekers et al., 2009), while a fourth study indicated a blunted increase in systolic and diastolic blood pressure in RU compared to NRU (Desrosiers et al., 2015).

Studies of repeated exposure to cannabis indicated that tachycardia lessens upon repeated administration of Δ9-THC or marijuana (Jones et al., 1976; Nowlan and Cohen, 1977), cannabis-induced tachycardia is less pronounced during active maintenance with Δ9-THC (Benowitz and Jones, 1975 (degree of tolerance observed: “Pulse rate”, 11.3%); Jones et al., 1976; Vandrey et al., 2013), and tolerance develops for the orthostatic but not supine hypotensive effects of Δ9-THC (Benowitz and Jones, 1975 (degree of tolerance observed: “Hypotension”, 44.8%); Jones et al., 1976).

Another study suggested that the intensity of the marijuana-induced tachycardia doesn’t differ between RU and NRU, while the duration of the effect is shorter in RU (Babor et al., 1975). Finally, only a study of repeated administration of Δ9-THC in a small sample of RU and over a short period failed to indicate less pronounced effects on pulse rate and blood pressure over time (Gorelick et al., 2013 (degree of tolerance observed: “Pulse rate”, 9.9%)).

3.6. Pharmacokinetics

A number of studies in recent years have investigated the pharmacokinetics of Δ9-THC and its major metabolites, with particular attention to cannabinoid plasma concentrations. Δ9-THC hydroxylation results in 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) and further oxidation in 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH), which may be glucuronidated to 11-nor-9-carboxy-delta-9-tetrahydrocannabinol glucuronide (THCCOO-glucuronide) (Grotenhermen, 2003). Research evidence indicates that RU with a history of recent cannabis exposure (Fabritius et al., 2013) or after a brief period of abstinence of 24 hours (D'Souza et al., 2008b; Ranganathan et al., 2009) have higher THC-COOH levels than NRU at baseline. However, consistent findings suggest that after a single intravenous administration of Δ9-THC RU and NRU do not differ in terms of Δ9-THC (Barkus et al., 2011; D'Souza et al., 2008b; Ranganathan et al., 2009) and THC-COOH levels (D'Souza et al., 2008b; Ranganathan et al., 2009). Similarly, RU and NRU do not differ in Δ9-THC, 11-OH-THC, and THC-COOH levels after administration of vaporized Δ9-THC (Ramaekers et al., 2016). In contrast, other studies indicate that after both marijuana smoking (Desrosiers et al., 2015; Ramaekers et al., 2009; Theunissen et al., 2012; Fabritius et al., 2013) and oral Δ9-THC administration (Bosker et al., 2012) RU have higher Δ9-THC, 11-OH-THC, and THC-COOH levels than NRU. However, after accounting for baseline levels, this difference remains significant only for some studies (Ponto et al., 2004) but not for others (Fabritius et al., 2013). A very recent study highlighted how differences in cannabinoid levels between RU and NRU may depend on the route of administration (Newmeyer et al., 2017a). In particular, this study indicated that, compared to vaporized Δ9-THC, oral administration of Δ9-THC is associated with higher 11-OH-THC levels only in NRU. Also, the higher the Δ9-THC levels after oral dosing, the higher is the intoxication experienced by NRU (Newmeyer et al., 2017a). Finally, a study conducting multiple evaluations of cannabinoid concentrations in RU suggested that Δ9-THC and 11-OH-THC levels steadily increase over 6 days of repeated dronabinol administration (Gorelick et al., 2013).

3.7. Other behavioral measures

Only a limited number of studies have focused on other behavioral effects of cannabis. A study of repeated dronabinol administration conducted in a small sample of RU indicated that Δ9-THC increases caloric intake, satiety, sleep satisfaction and efficiency, food craving for proteins and fats, but that these effects were reduced or no longer distinguishable from placebo in the 2^{nd} half of the study (Bedi et al., 2010; degree of tolerance observed: “Total daily caloric intake", 11.7%; "Sleep satisfaction", 15%). Also, RU in this study reported increased hunger and craving for carbohydrates only in the 2nd half of the study, with no significant effect on social behavior (Bedi et al., 2010). However, other studies in larger samples indicated that no tolerance develops to the effect of Δ9-THC on food intake (Haney et al., 1999; Hart et al., 2002) or sleep quality (Hart et al., 2002) over a period of repeated Δ9-THC administration (Haney et al., 1999) or during active maintenance with Δ9-THC (Hart et al., 2002). Also, one of these studies confirmed previous evidence that social behavior in RU doesn't change upon repeated exposure to Δ9-THC (Haney et al., 1999). Other evidence indicated that after a single administration of oral Δ9-THC RU exhibited less impairment in their driving skills compared to NRU (Bosker et al., 2012) or their performance was not significantly impaired (Newmeyer et al., 2017b).

3.8. Physiological and neurophysiological measures

A number of studies specifically investigated development of tolerance to the physiological (other than cardiac) and neurophysiological effects of cannabis. Jones et al. in 1976 indicated that administration of Δ9-THC and crude cannabis extract induce several responses in RU which lessen in magnitude upon repeated exposure including body temperature increase, skin temperature decrease, salivary flow decrease, intraocular pressure decrease as well as EEG alpha slowing and auditory-evoked potential amplitude decreases (Jones et al., 1976). Instead, in this study no tolerance developed to the decrease in serum haematocrit, haemoglobin, bilirubin, and plasma testosterone induced by repeated exposure to Δ9-THC and cannabis crude extract (Jones et al., 1976). Four subsequent studies confirmed tolerance to the acute effect of intravenous Δ9-THC administration (Cortes-Briones et al., 2015; D'Souza et al., 2012) or marijuana smoking (Böcker et al., 2010; Theunissen et al., 2012 (degree of tolerance observed: "P100 targets", 6.7%)) on specific electrophysiological measures in RU. In particular, while performing a task, RU showed reduced P300a peak latency (D'Souza et al., 2012), increased P100 amplitude (Theunissen et al., 2012), and lower inter-trial coherence and evoked power (Cortes-Briones et al., 2015) compared to NRU.

Studies by D'Souza and colleagues indicated that a single intravenous administration of Δ9-THC induced an increase in cortisol (D'Souza et al., 2008b; Ranganathan et al., 2009) and brain-derived neurotrophic factor (D'Souza et al., 2009) which was less pronounced in RU compared to NRU. Other evidence from the same group indicated that prolactin levels were lower in RU compared to NRU both before (D'Souza et al., 2008a; D'Souza et al., 2008b; Ranganathan et al., 2009) and after acute challenge with Δ9-THC (D'Souza et al., 2008b; Ranganathan et al., 2009). A previous study conducted in a smaller sample (Mendelson et al., 1984) had reported that acute administration of cannabis compounds, either orally or via smoking, did not significantly affect plasma prolactin levels in both RU and NRU (Cohen's *d*: 0.26).

Studies have also reported that marijuana smoking was associated with a reduction in breath-holding duration only in NRU (Farris and Metrik, 2016) while respiration rate and expired carbon monoxide did not differ between RU and NRU acutely exposed to Δ9-THC (Newmeyer et al., 2017a). Another study indicated that regional cerebral blood flow did not differ between RU and NRU after smoking marijuana (Ponto et al., 2004). Barkus et al. found that previous cannabis use did not modulate dopamine release following intravenous administration of Δ9-THC (Barkus et al., 2011).

Repeated Δ9-THC exposure had no effect on body weight in a study (Bedi et al., 2010). In contrast, repeated Δ9-THC exposure induced weight gain in a longer study, although no tolerance developed to weight gain over the study period (Jones et al., 1976).

4. DISCUSSION

To our knowledge, this is the first systematic review of all human studies examining whether tolerance develops to the acute effects of cannabis or its main psychoactive ingredient, Δ9-THC. Previous human studies have reported conflicting results in terms of acute effects of cannabis, especially on cognitive function (Hart et al., 2001; Ramaekers et al., 2006). Some authors have suggested that the apparent discrepancy was attributable to the different Δ9-THC content of the preparations study volunteers have been exposed to (Ramaekers et al., 2006). Although it is plausible that higher Δ9-THC content preparations would have a greater detrimental effect on neuropsychological performance, in line with the warnings about the potential health risk of increasing cannabis potency (higher Δ9-THC content) (Freeman and Swift, 2016), factors other than Δ9-THC content have been suggested to account for the apparent discrepant findings across studies (Nordstrom and Hart, 2006). In particular, Nordstrom and Hart have highlighted the importance of taking into account the cannabis use history of study volunteers when drawing conclusions regarding the acute effects of cannabis in man (Nordstrom and Hart, 2006). Of course, the two explanations are not mutually exclusive, as it has been suggested that among cannabis-naïve individuals higher Δ9-THC content may increase the likelihood of adverse psychological effects, such as anxiety, depression and psychotic symptoms (Hall, 2009). It is also worth noting that differing individual sensitivity to the effects of Δ9-THC and cannabis (Bhattacharyya et al., 2012b; Bhattacharyya et al., 2014) as well as previous exposure to different cannabis strains with varying ratio of different cannabinoids, with opposing effects (Bhattacharyya et al., 2015; Bhattacharyya et al., 2010) may also underlie these discrepant findings.

Overall, this review demonstrates that cannabis has less prominent or no effects on a number of behavioral and physiological measures in regular users (RU) compared to non-regular users (NRU). Also, the behavioral and physiological effects of cannabis lessen over repeated exposure and often become no longer distinguishable from placebo. Moreover, the acute effects of cannabis are less prominent during active maintenance with Δ9-THC. These effects are discussed in detail below.

4.1. Studies of single Δ9-THC or cannabis administration

Studies of acute cannabis-induced behavioral and physiological effects have differed widely in methodology, administering marijuana or Δ9-THC at differing doses, in various ways (e.g. in a cigarette to be smoked, as "brownie" to be eaten, as a preparation to be injected or inhaled) and assessing effects at varying time points post-administration. Also, they have investigated these effects in people with varying levels of previous cannabis use and potential tolerance to its effects, and who have used the drug more or less recently before testing. Thus, it is not surprising that such studies have often produced a mixed pattern of results.

Studies of a single dose of Δ9-THC or cannabis included in this review have specifically investigated if their acute effects differ as a function of previous cannabis exposure. In some of the studies there was no evidence to support the development of tolerance to the intoxicating effects of the drug (Bosker et al., 2012; D'Souza et al., 2012; D'Souza et al., 2008b; Lindgren et al., 1981). However, these studies recruited relatively small samples (Bosker et al., 2012; D'Souza et al., 2012; Lindgren et al., 1981) and/ or non-regular users (NRU) with a wide range of previous cannabis exposure (Bosker et al., 2012; D'Souza et al., 2012; D'Souza et al., 2008b). Studies conducted in larger samples and on individuals well differentiated in their pattern of regular or non-regular cannabis use found less pronounced and shorter intoxication in regular users (RU) compared to NRU (Lex et al., 1984; Fabritius et al., 2013; Ponto et al., 2004).

Studies examining the effects of a single dose of Δ9-THC or cannabis on cognitive function reported less pronounced impairments as a function of previous cannabis exposure in the domains of divided but not sustained attention (Desrosiers et al., 2015; Marks and MacAvoy, 1989; Ramaekers et al., 2009; Theunissen et al., 2012), verbal memory (Cohen and Rickles, 1974; D'Souza et al., 2008a; D'Souza et al., 2008b), and time perception (Sewell et al., 2013). Less clear is the effect of previous cannabis use on psychomotor ability over time, with studies suggesting development of tolerance to the detrimental effect of cannabis on psychomotor coordination (Desrosiers et al., 2015; Hart et al., 2002; Ramaekers et al., 2009; Ramaekers et al., 2016) but not on other psychomotor processes such as response speed, sustained attention, visual spatial skills and set shifting (Kirk and de Wit, 1999; Meyer et al., 1971). Also, two studies suggested that driving skills are less (Bosker et al., 2012) or not affected (Newmeyer et al., 2017b) in RU compared to NRU following a single oral dose of Δ9-THC. Finally, limited evidence suggests that tolerance doesn't develop to the effects of cannabis on working memory, risk-taking, impulse control, and executive functioning (Desrosiers et al., 2015; Ramaekers et al., 2016).

Over the last 10 years, studies have consistently shown that following acute intravenous administration of Δ9-THC (D'Souza et al., 2012; D'Souza et al., 2009; D'Souza et al., 2008b) or marijuana smoking (Desrosiers et al., 2015; Fabritius et al., 2013; Lex et al., 1984) the transient induction of perceptual alterations, psychotomimetic (D'Souza et al., 2012; D'Souza et al., 2009; D'Souza et al., 2008b) and anxiety symptoms (Desrosiers et al., 2015) as well as symptoms of confusion (Fabritius et al., 2013; Lex et al., 1984) is less pronounced in RU than NRU. Also, the more individuals have used cannabis in the past, the greater has been the tolerance to the acute psychotomimetic effects of Δ9-THC (Barkus et al., 2011).

Single or limited exposure to Δ9-THC or marijuana has been associated with lower tachycardia in RU compared to NRU in some (Desrosiers et al., 2015; Meyer et al., 1971; Ponto et al., 2004; Ramaekers et al., 2009; Lex et al., 1984) but not all studies (Kirk and de Wit, 1999; Lindgren et al., 1981; Renault et al., 1971). This discrepancy could be attributable to the low statistical power of studies failing to report development of tolerance to the cannabis-induced tachycardia. Also, limited evidence suggests that at higher Δ9-THC blood levels RU are more tolerant to the oral cannabis-associated tachycardia compared to NRU (Newmeyer et al., 2017a). Less clear is the effect on blood pressure, with only one (Desrosiers et al., 2015) out of four studies (Newmeyer et al., 2017a; Ponto et al., 2004; Ramaekers et al., 2009) suggesting a less prominent increase in systolic and diastolic blood pressure in RU compared to NRU.

Other studies of single Δ9-THC administration or limited exposure to marijuana suggest that RU develop tolerance to the effect of cannabis on electrophysiological function (Cortes-Briones et al., 2015; D'Souza et al., 2012; Theunissen et al., 2012; Böcker et al., 2010), cortisol (D'Souza et al., 2008b; Ranganathan et al., 2009), prolactin (D'Souza et al., 2008a; D'Souza et al., 2008b; Ranganathan et al., 2009), Brain-derived neurotrophic factor (D'Souza et al., 2009), and breath-holding duration (Farris and Metrik, 2016). Instead, respiration rate (Newmeyer et al., 2017a), regional cerebral blood flow (Ponto et al., 2004), and dopamine release (Barkus et al., 2011) didn't differ following acute administration of Δ9-THC as a function of previous cannabis exposure. However, the study by Barkus et al. was conducted in a small sample and was not designed explicitly to test the development of tolerance as a function of previous cannabis exposure (Barkus et al., 2011). Therefore, whether tolerance develops to the potential Δ9-THC-induced acute release of dopamine remains unclear.

4.2. Studies of repeated Δ9-THC or cannabis administration

For understandable reasons, monitoring the behavioral and physiological effects of Δ9-THC or cannabis upon repeated administration represents the best suitable research paradigm to investigate development of tolerance. Consistently, there is much more agreement between studies of repeated Δ9-THC or cannabis administration compared to studies of single Δ9-THC or cannabis administration with reference to the association between cannabis use and tolerance development. In particular, all such studies have shown development of tolerance to the intoxicating effects of cannabis in RU compared to NRU upon continuous exposure (Babor et al., 1975; Gorelick et al., 2013; Haney et al., 1999; Jones et al., 1976). Also, the intoxicating effect of Δ9-THC is greater at higher Δ9-THC plasma concentrations only in NRU (Newmeyer et al., 2017a). In contrast, the greater the extent to which RU have used cannabis in the past, the faster has been the decline in the intoxicating effects of cannabis (Nowlan and Cohen, 1977). Tolerance to the intoxicating effects of cannabis has been reported with both marijuana smoking (Desrosiers et al., 2015; Ramaekers et al., 2009; Theunissen et al., 2012) and vaporized cannabis (Ramaekers et al., 2016). However, limited evidence suggests that RU may display greater tolerance to the intoxicating effects of cannabis when it is administered orally compared to the vaporized route of administration (Newmeyer et al., 2017a).

Studies indicated relatively minor or no effects of repeated Δ9-THC administration in RU on a number of cognitive domains including learning, memory, vigilance, and psychomotor ability (Bedi et al., 2010; Haney et al., 1999; Jones et al., 1976). This absence of effect in RU might indicate the development of full tolerance. Intriguingly, tolerance to the cognitive effects of Δ9-THC was still evident even after a brief period of abstinence (Haney et al., 1999).

Repeated Δ9-THC or cannabis administration has been shown to blunt the mood changes associated with use of the drug only in one (Jones et al., 1976) out of three studies (Bedi et al., 2010; Meyer et al., 1971). However, evidence is too limited to draw any conclusion. Further research is needed to investigate whether upon repeated cannabis exposure tolerance develops to cannabis-associated psychosis-like symptoms and anxiety.

All (Babor et al., 1975; Benowitz and Jones, 1975; Jones et al., 1976; Nowlan and Cohen, 1977; Vandrey et al., 2013) but one study conducted in a small sample and over a short follow-up period (Gorelick et al., 2013) indicated less pronounced effects of repeated administration of Δ9-THC or marijuana on tachycardia (Babor et al., 1975; Benowitz and Jones, 1975; Jones et al., 1976; Nowlan and Cohen, 1977; Vandrey et al., 2013), and orthostatic hypotension (Benowitz and Jones, 1975; Jones et al., 1976). Also, repeated Δ9-THC administration has been associated with progressive tolerance to the effects of cannabis on body temperature, skin temperature, salivary flow, intraocular pressure, and electrophysiological function (Jones et al., 1976). Moreover, progressive tolerance has been shown to the effects of repeated Δ9-THC administration on food intake and sleep only in one (Bedi et al., 2010) out of three studies (Haney et al., 1999; Hart et al., 2002). Finally, other studies have indicated that repeated exposure to Δ9-THC has no effect on social behavior (Bedi et al., 2010; Haney et al., 1999) and body weight (Bedi et al., 2010) and no tolerance develops to its effects on haematocrit, haemoglobin, bilirubin, plasma testosterone, and body weight (Jones et al., 1976).

4.3. Neurobiological mechanisms underlying development of tolerance

Studies seem to indicate that after a brief period of abstinence of 24 hours, RU in the non-intoxicated state have higher levels of Δ9-THC metabolites compared to NRU (D'Souza et al., 2008b; Ranganathan et al., 2009). What is less clear is whether cannabinoid plasma concentrations differ after acute administration of Δ9-THC depending on the extent of previous cannabis use (Fabritius et al., 2013), with some studies indicating higher levels of Δ9-THC and its metabolites in RU compared to NRU (Bosker et al., 2012; Desrosiers et al., 2014a; Desrosiers et al., 2015; Ramaekers et al., 2009; Theunissen et al., 2012), and other studies reporting no difference (Barkus et al., 2011; D'Souza et al., 2008b; Ramaekers et al., 2016; Ranganathan et al., 2009). The discrepancy might be due to the different routes of Δ9-THC administration used in these studies, with only oral and smoke routes leading to higher cannabinoids levels in RU compared to NRU (Bosker et al., 2012; Desrosiers et al., 2014a; Desrosiers et al., 2015; Ramaekers et al., 2009; Theunissen et al., 2012), and not intravenous or vaporized exposure (Barkus et al., 2011; D'Souza et al., 2008b; Ramaekers et al., 2016; Ranganathan et al., 2009). The potential higher cannabinoid levels in RU are not surprising given Δ9-THC highly lipophilic nature and extended excretion in chronic or frequent cannabis users (Desrosiers et al., 2014a).

Some studies have indicated that the higher concentrations of Δ9-THC (Newmeyer et al., 2017c) and its metabolites (Fabritius et al., 2013) observed in RU compared to NRU following acute exposure were potentially due to the already higher cannabinoid levels in RU at baseline (Newmeyer et al., 2017c; Fabritius et al., 2013) and reflected recent exposure (Toennes et al., 2010). This was in line with evidence that Δ9-THC concentrations declined rapidly over the first few hours following cannabis use (Toennes et al., 2008; 2010). Also, the co-occurrence of higher concentrations of other cannabinoids in RU, such as cannabinol or cannabigerol (Sworwood et al., 2017), might be indicative of recent cannabis use independent of the experimental drug challenge (Newmeyer et al., 2016). Moreover, it has been suggested that the longer cannabinoid detection windows observed in RU compared to NRU following Δ9-THC smoking (Desrosiers et al., 2014b; Anizan et al., 2013; Himes et al., 2013) might suggest that RU smoked more efficiently (Toennes et al., 2008) rather than indicating significant changes in Δ9-THC pharmacokinetics.

The question arising is whether the higher cannabinoid levels in RU may be at least in part a consequence of modified biotransformation activities and be ultimately accountable for the development of tolerance observed following repeated exposure. Limited preclinical evidence indicates that repeated exposure to synthetic cannabinoids leads to tolerance through an alteration of the drug metabolizing enzyme system (Costa et al., 1996). Conversely, a large body of research seems to indicate that tolerance may develop also in the absence of pharmacokinetic changes and be attributable to pharmacodynamic events such as cannabinoid receptor type 1 (CB1) down regulation, receptor conformational change, and receptor internalization, with a subsequent decreased interaction of ligand and receptor (Ameri, 1999). However, CB1 receptor downregulation and related desensitization varies in rate and magnitude across the brain. For instance, CB1 receptor downregulation has been observed in the striatum, cerebellum and limbic forebrain, but not in the ventral mesencephalon, and some areas such as the hippocampus show faster and greater CB1 receptor downregulation and desensitization than other brain areas such as the basal ganglia (Ameri, 1999). In line with evidence from animal models (Rubino et al., 1997), this difference might explain why the development of tolerance follows different time courses and occurs to different extent in human studies reviewed here, with potential full tolerance developing for cognitive impairments whereas only partial tolerance develops for some physiological functions. For instance, regular users seem to show blunted responses to the amnestic but not to the euphoric effects of Δ9-THC, which may be mediated by different regions, the hippocampus and basal ganglia respectively (D'Souza et al., 2008b). Recent studies have indicated that RU may show blunted responses to the neurophysiological alterations induced by Δ9-THC in brain areas relevant to the manifestation of psychosis-like symptoms as well as verbal memory, response inhibition, attentional salience, and emotional processing (Colizzi et al., 2018a, in press; Colizzi et al., 2018b, in press).

4.4. Other substance use and tolerance

Psychostimulants such as cocaine and amphetamine induce a variety of behavioral and physiological effects, including psychoactive and cardiovascular effects as well as changes in appetite and body temperature (Kiyatkin, 2013; Frazer et al., 2018; Mladěnka et al., 2018). Preclinical evidence suggests that following sustained exposure to these drugs, tolerance develops for most of their effects (Zernig et al., 2007)). Similarly, evidence from human studies suggests that tolerance to cocaine (Mendelson et al., 1998) and methamphetamine (Strakowski et al., 2001) physiologic, neuroendocrine, and subjective effects may occur as a function of repeated exposure. Pharmacodynamic mechanisms have been suggested to explain the development of tolerance to the effects of psychostimulant drugs, such as alterations in dopamine release, uptake, transporter, and corresponding tone (Ferris et al., 2012). However, as for cannabis, although the accumulation from regular exposure might account for the higher plasma levels of cocaine and amphetamine observed in some experimental studies, the possibility of pharmacokinetic alterations cannot be ruled out (McMillan, 1991).

Studies included in this review have tried to take into account the confounding effects of other psychostimulant use. However, the possible synergistic effects of cannabis and other psychostimulant drugs on tolerance development deserve further study. Preclinical studies have shown how repeated cannabinoid administration blunts the meso-accumbens dopamine response to an acute challenge with cannabinoid agonists but also to an acute challenge with cocaine and amphetamine, suggesting that tolerance to the effects of Δ9-THC may lead to cross-tolerance for the effects of other psychostimulant drugs (Pistis et al., 2004).

4.5. Implications for psychosis and Cannabis Use Disorder

What does this mean in terms of the development of a Cannabis Use Disorder (CUD) or psychosis in response to regular cannabis use? Development of tolerance to the intoxicating effects of cannabis, especially effects that are pleasurable, is consistent with a need to use progressively greater amounts of cannabis recreationally in order to get the same enjoyable effects, leading in turn to the development of a CUD. In those who end up developing a CUD but not a psychotic disorder, it is also likely that a similar progressive attenuation of the negative effects, in particular the psychotomimetic effects of cannabis would have occurred, thereby supporting continued use. This is consistent with a growing body of evidence that the risk of a CUD is higher among individuals experiencing early positive reactions to cannabis, possibly reflecting individual differences in the responsiveness of the mesolimbic dopamine system to the reinforcing effects of substance administration (Fergusson et al., 2003), while negative reactions are more likely to predict cessation of use (Sami et al., 2018). However, in those who end up developing a psychotic disorder or experiencing its relapse following continued cannabis use, independent, replicated evidence suggests that the risk of onset of psychosis (Colizzi and Murray, 2018; Moore et al., 2007; Sami and Bhattacharyya, 2018) or its relapse (Schoeler et al., 2016; Colizzi et al., 2016a) is linked to regular, frequent use, arguing against the development of tolerance to the psychotomimetic effects in these individuals. Whether this means that in such individuals, tolerance may selectively be developing to certain effects of cannabis and not to the psychotomimetic effects remains to be tested. Further studies are also needed to clarify potential biological differences between cannabis users who develop tolerance to the effects of the drug and cannabis users who develop psychotic or cannabis use disorders. The possibility that cannabis users who develop tolerance to the acute psychotomimetic effects of Δ9-THC are still at increased risk of psychosis cannot be ruled out.

4.6. Methodological limitations

Groups of regular (RU) and non-regular cannabis users (NRU) differed considerably across studies in terms of their pattern and frequency of cannabis use prior to assessment as well as dose and route of administration during the experiment (see methodological quality of studies in Table 2), limiting the comparison of the findings across the domains investigated. These aspects were partially mitigated in studies of repeated Δ9-THC or cannabis exposure, as the tolerance phenomenon was investigated in a controlled environment where subjects received standardized amounts of cannabis or its main active ingredient over a time period. Conversely, it represented a substantial limitation in studies of single Δ9-THC or cannabis exposure, where the tolerance manifestation, if present, followed a single administration and was modulated by previous cannabis exposure itself of study participants. This would explain the higher consistency and evidence of tolerance among studies of repeated Δ9-THC or cannabis exposure, potentially accounting for discrepancies among studies of single Δ9-THC or cannabis exposure. Independent of these explanations, differences in sample size across studies might also explain the inconsistent evidence for the development of tolerance to the intoxicating and cardiac effects of cannabis in studies of single Δ9-THC or cannabis exposure. The largest of these studies (Ponto et al., 2004) indicated tolerance development for both domains with a large effect size. However, the available data didn't allow a systematic power calculation across studies. Moreover, very limited evidence seems to suggest that the development of tolerance differed according to the route of administration, with higher tolerance when cannabis is administered orally compared to other routes of administration (Newmeyer et al., 2017a). However, data was too limited to draw any conclusion.

Also, the large majority of the studies reviewed here recruited a group of RU presenting with recent cannabis use and often a urine drug screen positive for Δ9-THC, as this represented an inclusion criterion to differentiate participants with regular versus non-regular cannabis use. Thus, as stated before, this limits the possibility of disentangling whether the higher levels of Δ9-THC and its metabolites observed among RU in some of these studies represent an alteration in pharmacokinetic processes such as distribution, metabolism and elimination, or just the consequence of Δ9-THC accumulation within the organism. Both phenomena may coexist, as indicated by cellular studies suggesting complex relationship between Δ9-THC accumulation and its metabolism in the brain (Monnet-Tschudi et al., 2008). Likewise, it is not clear whether tolerance to the effects of Δ9-THC would persist after an adequate period of abstinence. Limited evidence reviewed here suggests that RU are still tolerant to the cognitive effects of Δ9-THC on cognitive processes after 4 days of abstinence preceding the drug challenge (Haney et al., 1999). Also, other evidence suggests that tolerance to the intoxicating effects of cannabis upon repeated exposure shows only partial recovery after 1 week of abstinence (Nowlan and Cohen, 1977). However, despite being identified as a crucial pharmacodynamic mechanism underlying tolerance development following sustained cannabis exposure (Ameri, 1999), CB1 receptor downregulation has been shown to be selective and rapidly reversed after just two days of monitored abstinence from cannabis (D'Souza et al., 2016). Future studies need to examine whether tolerance persists after longer periods of abstinence preceding the acute challenge and its relationship with downregulation of CB1 receptor across different brain areas.

An alternative explanation for the blunted effects of Δ9-THC in RU is that RU, especially when not developing psychosis-like symptoms, may be innately protected from some of the detrimental effects of cannabis. It has been shown that monozygotic twins are more likely to report similar experiences when exposed to cannabis compared to dizygotic twins (Lyons et al., 1997). Also, inter-individual variation in the availability of cannabinoid receptors (Bhattacharyya et al., 2017) as well as genetic variation in cannabinoid (Colizzi et al., 2015a; Taurisano et al., 2016) and dopamine signalling (Bhattacharyya et al., 2014; Colizzi et al., 2015b; Colizzi et al., 2015c) have been linked to variation in the extent of psychotomimetic and neurocognitive effects of cannabis and Δ9-THC. However, the higher concordance within studies of repeated Δ9-THC or cannabis administration compared to studies of single Δ9-THC or cannabis administration in reporting an association between regular cannabis use and development of tolerance argues against the possibility that tolerance in RU may be explained by genetically determined differences.

4.7. Future directions and conclusions

Available evidence suggests that the effects of acute marijuana or Δ9-THC administration are less prominent in individuals with a regular pattern of cannabis use compared to non-regular users. Cognitive function appears to be the domain most likely to demonstrate tolerance upon repeated exposure, with some evidence of full tolerance indicating a complete absence of acute effect. The acute intoxicating and cardiac effects of Δ9-THC are also blunted upon regular exposure. Similar but limited evidence also suggests blunted acute psychotomimetic effects of Δ9-THC in individuals using cannabis regularly. The degree of tolerance in these domains varies, with generally an evidence of partial tolerance that is presence of some, albeit attenuated acute effects. Less clear or very limited is the evidence supporting the development of tolerance for other behavioral, physiological, and neural effects of cannabis.

The adverse effects of repeated Δ9-THC administration on neurons may occur through a combination of pathways involving cannabinoid receptor activation (Colizzi et al., 2016b), accumulation of cannabinoids and their metabolites, and upregulation of neuroinflammatory cytokines (Monnet-Tschudi et al., 2008). Thus, tolerance may play a relevant role in the cascade of neurobiological events leading to disorders affecting brain chemistry and circuitry. Further studies are needed to better understand the neurobiological mechanisms underlying the development of tolerance upon repeated cannabis exposure in man.

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Figure 1. PRISMA flowchart of search strategy for systematic review

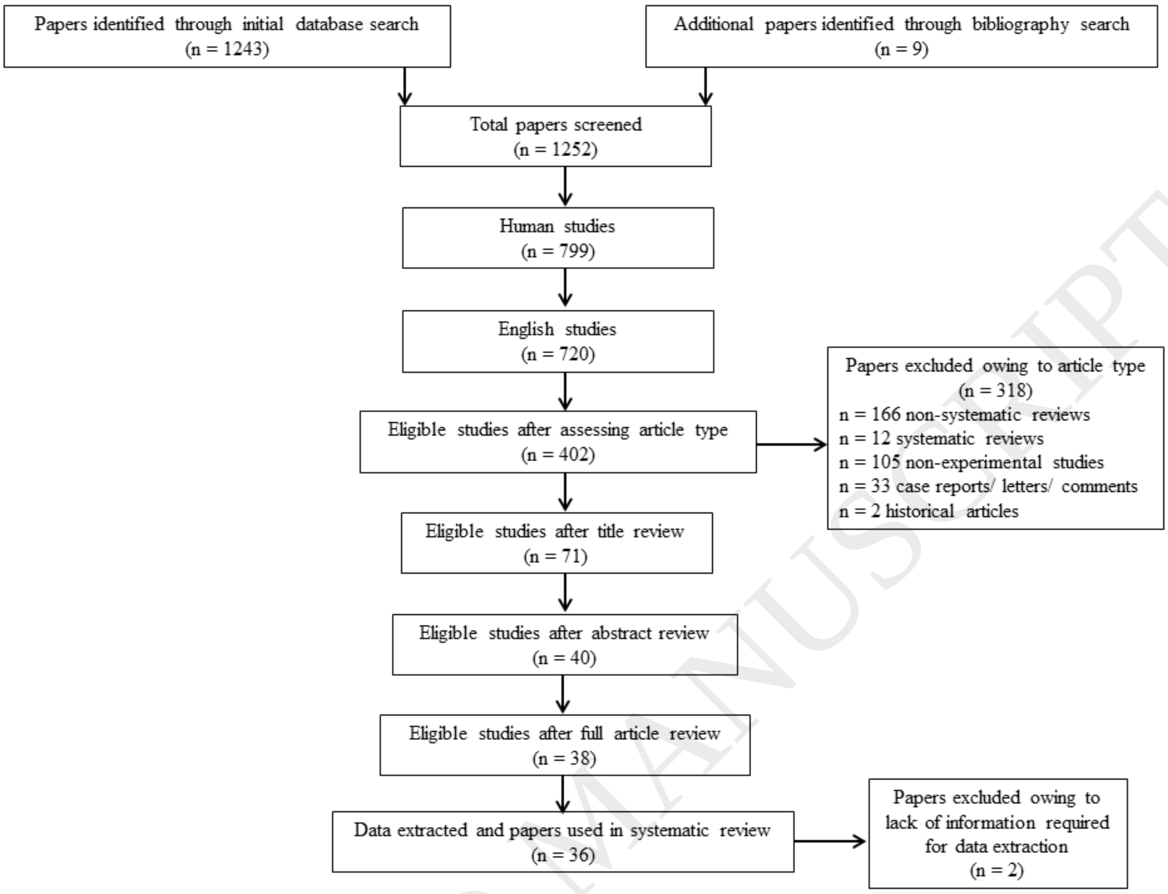

Table 1. Summary of human studies investigating development of tolerance in cannabis users

Study	Aim of study	Population	n	Outcome measure (test name or description)	Behavioral results	Laboratory and physiological results
Meyer et al., 1971	Effects of MJ on subjective effects, psychopathology, cognition, and cardiac parameters	1. RU (n=6); 2. NRU (n=6)	12	Sympathetic arousal (Finger sweat), "psychedelic experience" (DEQ), dependence (Hidden patterns), attention (CPT), psychomotor ability (DSST), time sense (TPT), focus and distraction (SCWT), hand-eye coordination (Pursuit rotor), mood states (POMS), "High" (PR)	1. Subjective effects, NS; 2. Mood states, NS (apart from **"vigor" factor, RU > NRU**); **3. Impaired attention, RU < NRU (MJ effect only in NRU)**; 4. Other cognitive performance, NS	**5. "High" by the end of experiment (PR at ~1h), RU < NRU**
Renault et al., 1971	Effects of MJ on cardiac parameters	1. RU (n=6); 2. NU (n=4)	10	PR	NA	Tachycardia, NS
Cohen and Rickles, 1974	Effects of MJ on cognition	1. PLB NRU; 2. PLB RU; 3. MJ NRU; 4. MJ RU	30	Learning (a list of 9 word paired associate consisting of a CVC trigram – nonsense syllable – and a word)	**Learning, trend level significance, PLB NRU > other groups, MJ NRU < other groups**	NA
Babor et al., 1975	Effects of MJ on intoxication and cardiac parameters	1. RU (n=11); 2. NRU (n=7)	18	Intoxication (7-point bipolar adjective scale, "stoned" vs "straight"), PR	**1. Intoxication, trend level significant ↓ upon continuous MJ exposure only in RU**	**2. Tachycardia: duration (effect 25 min after use) ↓only in RU,** intensity (effect immediately after use) NS
Benowitz and Jones, 1975	Effects of Δ9-THC and MJ on cardiac parameters	CBSU	12	PR, supine BP, standing BP, BP after exercise, BP during Valsalva maneuver, BP in the supine position placing one hand to the wrist in ice water for 30 sec (Cold pressor test), ECG, plasma volume (Evans Blue dye method)	NA	1. Supine hypotension, NS; **2. Orthostatic hypotension, ↓ over study period**; **3. MJ-induced tachycardia, ↓ over Δ9-THC maintenance**
Jones et al., 1976	Effects of Δ9-THC, crude extract, and MJ on subjective effects, intoxication, psychopathology, cognition, cardiac parameters, sleep, and other physiological parameters	RU	53	Mood (POMS), subjective effects (SCL-90), cognitive and psychomotor function, "psychedelic experience" (DEQ),sleep, PR, BP, Salivary flow, intraocular pressure, skin and body temperature, EEG, weight, haematocrit, haemoglobin, bilirubin, testosterone	**1. High-dose intoxication, ↓ after 96h of minimal but continuous intoxication; 2. Dose-dependent effect on intoxication no longer evident after 12 days; 3. Sedation, ↓ over study period;** 4. Good feelings, NS; 5. Withdrawal symptoms, NS; **6. Increase in sleep duration and quality, ↓ over study period; 7. Cognitive and psychomotor impairment, ↓ over study period; 8. Mood changes, ↓ over study period**	**9. Skin temperature decrease, 10. Salivary flow decrease, 11. Tachycardia, 12. Reduced BP** (supine, NS)**, 13. Intraocular pressure decrease, 14. Body temperature increase, and 15. EEG alpha slowing and auditory-evoked potential amplitude decreases, all ↓ over study period;** 16. Weight gain, NS; 17. Serum haematocrit and haemoglobin decrease, NS; 18. Bilirubin decrease, NS 19. Plasma testosterone decrease, NS; **20. MJ-induced tachycardia, ↓ in intensity and duration over Δ9-THC maintenance**
Nowlan and Cohen, 1977	Effects of MJ on intoxication and cardiac parameters	1. LU/ LMU (n=14-16); 2. HMU (n=7-8); 3. HU (n =7-8)	30	"High" (7-point bipolar adjective scale, "straight" or non-intoxicated vs highest ever been on MJ), PR	**1. "High", ↓ over study period in whole group, partial recovery after 1-week abstinence; 2. "High", ↓ during 1st week in HU vs other groups combined; 3. "High", more rapid and sharp↓ in HU than other groups, 4. "High", ↓ duration in HU vs other groups**	**5. Tachycardia, ↓ over study period in whole group, partial recovery after 1-week abstinence; 6. Tachycardia, LU/ LMU > HM > HU during 1st week; 7. Tachycardia, more rapid ↓ in HU and MHU than LU**
Lindgren et al., 1981	Effects of Δ9-THC and MJ on intoxication and cardiac parameters	1. RU (n=9); 2. NRU (n=9)	18	"High" (10-point scale, no effect vs maximum effect the subject could imagine), PR	1. "High", NS	2. Tachycardia, NS
Lex et al., 1984	Effects of Δ9-THC on subjective effects, cardiac parameters, and psychopathology	1. RU (n=9); 2. NRU (n=10)	19	PR, intoxication (11-point scale, from " not high at all" to "highest ever"), confusion (POMS)	**1. Intoxication: duration (effect 90 min after use) ↓only in RU; 2. Confusion: ↑ only in NRU 30 min after use; 3. Correlations between PR, intoxication, and confusion only in NRU 15 and 30 min after use**	**4. Tachycardia: duration (effect 90 and 180 min after use) ↓only in RU**

Mendelson et al., 1984	Effects of Δ9-THC on the endocrine system	1. RU (n=8); 2. IU (n=7); 3. NRU (n=8)	23	Prolactin	NA	Prolactin, NS
Marks et al., 1989	Effects of MJ on cognition	1. NRU (n=6); 2. NU (n=6)	12	Divided attention (eight 5-min blocks, each containing 30 signals in random order but with an equal probability of either central or peripheral signals occurring)	**Divided attention: peripheral signal detection, dose-dependent impairment NRU < NU**; central signal detection, NS	NA
Haney et al., 1999	Effects of Δ9-THC on subjective effects, cognition, food intake, and social behavior	RU	12	Drug effect and physical symptoms (50-item VAS, 100-mm line, "not at all" to "extremely"), "psychedelic experience" (DEQ), learning, memory, vigilance, and psychomotor ability (DSST, DAT, RIT, Immediate and Delayed DRT), food intake, verbal and non-verbal social behavior	**1. Subjective effects ↓ over study period; 2. Drug-effect (dose strength, dose liking, willingness to take the dose again) ↓ over study period;** 3. Food intake, NS; 4. Social behavior, NS; 5. **No effect on cognition** apart from DAT performance impaired on day 1 at high Δ9-THC dose	NA
Kirk and De Wit, 1999	Effects of Δ9-THC on subjective effects, cognition, and cardiac parameters	1. RU (n=11); 2. NRU (n=10)	21	MJ-like effects and sedation (53-item version of the ARCI), VAS ("not at all" to "very"); "psychedelic experience" (DEQ), overall experience (End-of-session questionnaire), psychomotor ability (DSST), PR	**1. Lower dose, "Feel" and "High" only in RU; 2. Higher dose, sedative-like effects, RU < NRU; 3. Higher dose, stimulant-like effects ↓ only in NRU; 4. Higher dose, liking effects↓ only in NRU;** 5. Psychomotor performance, NS; 6. Other subjective effects, NS; 7. Willing to take again, NS	8. Tachycardia, NS
Hart et al., 2002	Effects of Δ9-THC and MJ on subjective effects, cognition, sleep, and food intake	RU	12	Drug effect and physical symptoms (50-item VAS, 100-mm line, "not at all" to "extremely"), "psychedelic experience" (DEQ), learning, memory, vigilance, and psychomotor ability (DSST, RAT, DAT, RIT, Immediate and Delayed DRT)	1. **MJ-induced subjective effects ↓ over Δ9-THC maintenance; 2. MJ-induced impairment in DRT ↓over Δ9-THC maintenance and at higher dose,** but other psychomotor performance NS; 3. Reinforcing effects, NS; 4. Food intake, NS; 5. Sleep, NS	NA
Ponto et al., 2004	Effects of MJ on intoxication, cardiac parameters, pharmacokinetics, and other physiological parameters	1. RU (n=12); 2. NRU (n=24)	36	"High", PR, BP, arrival time of bolus, rCBF (pharmacokinetics of $[^{15}O]$ water), Δ9-THC levels	**1. "High" and related duration, RU < NRU**	**2. Δ9-THC levels, RU > NRU, even correcting for baseline; 3. Tachycardia, related change, and duration, RU < NRU; 4. RPP, related change, and duration, RU < NRU;** 5. Systolic BP, NS; 6. Diastolic BP, NS; 7. Arrival time of bolus, NS; 8. rCBF, NS; **9. Correlations between "high" and cardiovascular function, significant only in NRU; 10. Correlations between bolus arrival time/ rCBF and cardiovascular function, NRU > RU**
D'Souza et al.,2008a	Effects of Δ9-THC on cognition and endocrine system	1. RU (n=11); 2. NRU (n=17)	28	Verbal learning and immediate and delayed recall (VLT), vigilance (CPT), executive function, spatial memory, and visual recognition memory (CANTAB), speed and accuracy (MOT), akathisia and drug-induced Parkinsonism (BARS), prolactin	**1. Impaired immediate recall (in combination with haloperidol), RU < NRU (effect only in NRU);** 2. Impaired attention, NS; **3. Impaired spatial working memory, RU < NRU;** 4. other performance, NS	5. Prolactin, NS **(RU < NRU at baseline)**
D'Souza et al.,2008b	Effects of Δ9-THC on intoxication, psychopathology, cognition, cardiac parameters, pharmacokinetics, and endocrine system	1. RU (n=30); 2. NRU (n=22)	52	Psychotomimetic symptoms (PANSS), perceptual alterations (CADSS), anxiety and intoxication (VAS), Verbal learning and immediate and delayed recall (VLT), vigilance (CPT); PR, Δ9-THC and THC-COOH levels, cortisol, prolactin	**1. Perceptual alterations, RU < NRU; 2. Psychotomimetic symptoms, RU < NRU;** 3. "High", NS; **4. Anxiety, RU < NRU;** 5. "Calm and relaxed", NS; **6. Impaired immediate recall and delayed free recall, RU < NRU** (RU > NRU at baseline)**;** 7. Delayed recognition recall, NS; 8. Impaired attention, NS	9. Tachycardia, NS; 10. Δ9-THC levels, NS; 11. THC-COOH levels, NS (**RU > NRU at baseline**); **12. Cortisol increase, RU < NRU; 13. Prolactin (overall), RU < NRU**

D'Souza et al.,2009	Effects of Δ9-THC on psychopathology, cognition, and neurochemistry	1. RU (n=9); 2. NRU (n=14)	23	Psychotomimetic symptoms (PANSS), perceptual alterations (CADSS), "High" (VAS), spatial memory, BDNF	**1. Perceptual alterations, RU < NRU; 2. Psychotomimetic symptoms, RU < NRU; 3. Impaired spatial working memory, RU < NRU**	**4. Increased BDNF, RU < NRU (increase only in NRU)**
Ramaekers et al., 2009	Effects of Δ9-THC MJ on intoxication, cognition, cardiac parameters, and pharmacokinetics	1. RU (n=12); 2. NRU (n=12)	24	"High" (VAS, 100-mm line), psychomotor ability (CTT), attention (DAT), motor impulsivity (SST), executive function and planning (TOL), PR, BP, Δ9-THC, 11-OH-THC, and THC-COOH levels	**1. "High", RU < NRU; 2. CTT impaired performance, RU < NRU (effect only in NRU); 3. DAT impaired performance, ↑ during 1st h only in NRU;** 4. Other performance, NS; **5. Increase in the proportion of cognitive impairment observations in NRU for all domains, in RU only for SST at high Δ9-THC levels (>10 ng/ml)**	**6. PR, RU < NRU;** 7. BP, NS; **8. Δ9-THC, 11-OH-THC, and THC-COOH levels, RU > NRU**
Ranganathan et al., 2009	Effects of Δ9-THC on pharmacokinetics and endocrine system	1. RU (n=40); 2. NRU (n=36)	76	Δ9-THC and THC-COOH levels, cortisol, prolactin	NA	**1. Dose-dependent cortisol increase, RU < NRU; 2. Prolactin (overall), RU < NRU;** 3. Δ9-THC levels, NS; 4. THC-COOH levels, NS **(RU > NRU at baseline)**
Bedi et al., 2010	Effects of dronabinol on subjective effects, psychopathology, cognition, sleep, and food intake	RU	7	Food intake, weight, subjective hunger and satiety (HSQ), food cravings (FDQ), mood (VAS), "psychedelic experience" (DEQ), Sleep (Nightcap sleep monitor and sleep quality VAS), learning, memory, vigilance, and psychomotor ability (DSST, RAT, DAT, RIT, Immediate and Delayed DRT), verbal and non-verbal social behavior	**1. Increased caloric intake, ↓ over study period (not different from PLB in 2nd half of study period); 2. Sleep satisfaction, ↑ over 1st half of study period only;** 3. Subjective effects, NS, 4. Cognition, NS; 5. Social behavior, NS; **6. Satiety, ↑ over 1st half of study period only** (hunger ↑ over 2nd half of study period only, other parameters, NS); **7. Food craving, ↑ for protein/ fat over 1st half of study period only** (for carbohydrate over 2nd half of study period only)	**8. Sleep efficiency ↑ only over 1st half of study;** 9. Weight, NS
Böcker et al., 2010	Effects of Δ9-THC on electrophysiology	1. RU (n=12); 2. NRU (n=11)	23	EEG, ERP task (visual selective attention Task; SFD80, FSP, OSN)	NA	**1. SFD80, RU < NRU; 2. OSN, ↓ linearly with cannabis dose only in NRU; 3. FSP, RU < NRU**
Barkus et al., 2011	Effect of Δ9-THC on psychopathology, pharmacokinetics, and neurochemistry	CBSU	9	Psychotomimetic symptoms (PANSS), dopamine release ([123I]IBZM SPET scanning session, 185 MBq), Δ9-THC levels	**1. Positive symptoms, negative correlation with previous cannabis use**	2. Dopamine release, NS; 3. Δ9-THC levels (AUC), NS
Bosker et al., 2012	Effect of Δ9-THC on intoxication, pharmacokinetics, and driving	1. RU (n=12); 2. NRU (n=12)	24	Driving (Road-tracking test, SDLP, TSA), impairments during on-the-road driving (SFST), "high" (VAS, 100-mm line, "not at all" to "most ever"), Δ9-THC, 11-OH-THC, and THC-COOH levels	**1. SDLP impairment, RU < NRU** (however, 25% RU still displaying driving impairments ≥ Blood alcohol concentrations of 0.5 mg/ml (0.05 g%)**; 2. TSA impairment, RU < NRU;** 3. SFST, NS; 4. "high", NS	**5. Δ9-THC, 11-OH-THC, and THC-COOH levels, RU > NRU**
D'Souza et al.,2012	Effect of Δ9-THC on intoxication, psychopathology, and electrophysiology	1. RECU (n=14); 2. NRECU (n=12)	26	Psychotomimetic symptoms (PANSS), perceptual alterations (CADSS), "High" (VAS), EEG, ERP task (three-stimulus auditory "oddball" P300 task)	**1. Perceptual alterations, RECU < NRECU; 2. Psychotomimetic symptoms, RECU < NRECU;** 3. Behavioral measures, NS	4. P300b amplitude and latency, NS; 5. P300a amplitude, NS; **6. P300a peak latency, RECU < NRECU**
Theunissen et al., 2012	Effect of MJ on subjective effects, intoxication, cognition, pharmacokinetics, and electrophysiology	1. RU (n=12); 2. NRU (n=12)	24	"High" (VAS, 100-mm line, "not at all" to "maximally high"), EEG, ERP task (DAT, P100 and P300; SST, N200), Δ9-THC, 11-OH-THC, and THC-COOH levels	**1. "High" (immediately after smoking), RU < NRU; 2. DAT impaired performance, RU < NRU (effect specific to NRU);** 3. Behavioral measures, NS	**4. Δ9-THC, 11-OH-THC, and THC-COOH levels, RU > NRU; 5. P100 amplitude, ↓ in NRU (while trend level significant ↑ in RU);** 6. P100 latency, NS; 7. P300, NS; 8. N200, NS

Fabritius et al., 2013	Effect of Δ9-THC on intoxication, psychopathology, and pharmacokinetics	1. RU (n=23); 2. NRU (n=25)	48	Subjective effects (VAS, 100-mm line), Δ9-THC, 11-OH-THC, and THC-COOH levels	**1. Intoxication duration RU < NRU; 2. Confusion intensity and duration, RU < NRU**	**3. Δ9-THC, 11-OH-THC, and THC-COOH levels, RU > NRU at baseline for all, after administration for 11-OH-THC and THC-COOH** (however NS after correcting for baseline levels)
Gorelick et al., 2013	Effect of Δ9-THC on subjective effects, cardiac parameters, and pharmacokinetics	RU	13	Subjective effects (VAS, 100-mm line), PR, BP, Δ9-THC and 11-OH-THC	**1. Intoxication ("high" and "stoned") and "Good drug effect", ↓ over study period**	2. Hypotension, NS; 3. Tachycardia, NS; 4. Δ9-THC and 11-OH-THC levels, increasing over time
Sewell et al., 2013	Effect of Δ9-THC on cognition	1. RECU (n=10); 2. NRECU (n=34)	44	TET, TPT	**1. TET impairment, effect only in NRECU; 2. TPT impairment, effect only in NRECU**	NA
Vandrey et al., 2013	Effect of Δ9-THC and dronabinol on subjective effects and cardiac parameters	RU	13	Withdrawal (MWC), sleep (diary and VAS), craving (MCQ), drug effects (ARCI), PR	1. Subjective effects, NS	**2. Cannabis-induced tachycardia, ↓ over high-dose Δ9-THC maintenance**
Cortes-Briones et al., 2015	Effect of Δ9-THC on electrophysiology	1. RECU (n=9); 2. NRECU (n=11)	20	EEG, ASSR task (three-stimulus auditory "oddball" inter-trial coherence and evoked power task)	NA	**1. Inter-trial coherence, RECU < NRECU at trend level significance; 2. Evoked power, RECU < NRECU**
Desrosiers et al., 2015	Effects of Δ9-THC MJ on subjective effects, intoxication, psychopathology, cognition, cardiac parameters, and pharmacokinetics	1. RU (n=14); 2. NRU (n=11)	25	"High" (VAS, 100-mm line), psychomotor ability (CTT), attention (DAT), working memory (N-Back task), risk taking and impulsivity (BART, MDMQ, BIS, ZKPQ, RPQ), BP, PR, Δ9-THC levels	**1. "High" and anxiety, RU < NRU; 2. Duration of subjective effects ("difficulty concentrating", "altered sense of time", "feel hungry", "feel thirsty", "shakiness/ tremulousness", "dry mouth or throat"), RU < NRU; 3. CTT impaired performance, RU < NRU; 4. DAT, hits, RU > NRU; 5. DAT, ↑ tracking errors, false alarms, and reaction times only in NRU;** 6. N-Back performance, NS **(however, N-Back RT decrease, RU < NRU;** 7. BART, NS; **8. Positive correlations between BART, BIS, ZKPQ, and RPQ only in NRU (some at trend level significance)**	**9. Δ9-THC levels, RU > NRU; 10. Tachycardia, RU < NRU; 11. Increased systolic and diastolic BP, RU < NRU**
Farris et al., 2016	Effects of Δ9-THC MJ on breath-holding duration	1. RU; 2. NRU	88	Breath-holding task (index of respiratory distress intolerance), puff count	1. Puff count, NS	**2. Post-smoking breath-holding duration, ↓ only in NRU**
Ramaekers et al., 2016	Effects of Δ9-THC on intoxication, cognition, and pharmacokinetics	1. LU (n=33); 2. LMU (n=41); 3. MHU (n=23); 4. HU (n=25)	122	Intoxication (VAS,100-mm line, "no intoxication" to "extremely intoxicated"), psychomotor ability (CTT), attention (DAT), motor impulsivity (SST), executive function and planning (TOL), Δ9-THC, 11-OH-THC, and THC-COOH levels	**1. CTT impaired performance, ↓ with increasing frequency of CBS use;** 2. Other performance, NS; **3. Intoxication, ↓ with increasing frequency of CBS use at trend level significance**	4. Δ9-THC, 11-OH-THC, and THC-COOH, NS
Newmeyer et al., 2017a	Effects of Δ9-THC on subjective effects, intoxication, cardiac parameters, pharmacokinetics, and other physiological	1. RU (n=11); 2. NRU (n=9)	20	Subjective effects (VAS), PR, BP, respiration rate, expired CO (Breath CO monitor)	**1. "Good drug effect", "high", and "stoned", oral effects only in NRU; 2. Willingness to drive, ↓ only in NRU after oral dosing; 3. CBS craving, ↓ only in RU after smoking and/ vs vaporization (baseline-adjusted); 4. "Good drug effect" and "stoned", vaporization > oral only in RU; 5. "Good drug effect" positive correlation**	**7. Δ9-THC and 11-OH-THC levels, RU > NRU; 8. 11-OH-THC levels, oral > vaporized in NRU only; 9. Tachycardia positive correlation with Δ9-THC levels after oral dosing only in NRU;** 10. BP, NS; 11. Respiration rate, NS; 12. Expired CO, NS

	parameters				**with Δ9-THC and 11-OH-THC levels after oral dosing only in NRU; 6. "High" positive correlation with Δ9-THC levels after oral dosing only in NRU**	
Newmeyer et al., 2017b	Effects of Δ9-THC on pharmacokinetics	1. RU (n=11); 2. NRU (n=9)	20	Impairments during on-the-road driving (SFST: OLS, WAT)	**1. OLS impairment, oral effect only in NRU; 2. WAT impairment, oral effect only in NRU; 3. OLS and WAT impairment positive correlation with Δ9-THC and 11-OH-THC levels after oral dosing only in NRU**	**4. Δ9-THC levels, RU > NRU; 5. Δ9-THC levels decrease, RU < NRU**

MJ, marijuana; Δ9-THC, delta-9-tetrahydrocannabinol; RU, regular users; NRU, non-regular users; IU, intermittent users; PLB, placebo; CBSU, cannabis users; LU, light users; LMU, low moderate users; HMU, high moderate users; HU, heavy users; RECU, recent users; NRECU, non-recent users; DEQ, Katz-Waskow subjective Drug Effects Questionnaire; CPT, Continuous Performance Test; DSST, Digit-Symbol Substitution Test; TPT, Time Perception Test; SCWT, Stroup Color-Word interference Test; POMS, Psychiatric Outpatient Mood Scale; PR, pulse rate; CVC trigram, consonant, vowel, and consonant trigram; BP, blood pressure; sec, seconds; ECG, electrocardiogram; EEG, electroencephalogram; SCL-90, Symptom Checklist-90; VAS, Visual Analogue Scale; DAT, Derived Attention Task; RIT, Rapid Information Task; DRT, Digit-Recall Task; SFD80, Spatial Frequency-Dependent potential at about 80 ms; OSN, Occipital Selection Negativity; FSP, Frontal Selection Positivity; TET, Time Estimation Task; TPT, Time Production Task; ARCI, Addiction Research Center Inventory; RAT, Repeated Acquisition Task; rCBF, regional Cerebral Blood Flow; PANSS, Positive and Negative Syndrome Scale; CADSS, Clinician Administered Dissociative Symptoms Scale; VLT, Verbal Learning Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; MOT, Motor Screening Task; BARS, Barnes Akathisia Rating Scale; BDNF, Brain-Derived Neurotrophic Factor; CTT, Critical tracking task; SST, Stop-Signal Task; TOL, Tower of London; THC-COOH, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol; HSQ, Hunger-Satiety Questionnaire; FDQ, Food Desirability Questionnaire; SDLP, TSA, Time to speed adaption; Standard Deviation of Lateral Position; SFST, Standardized Field Sobriety Test; 11-OH-THC, 11-hydroxy-delta-9-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; ERP task, Event-related potential task; MWC, Marijuana Withdrawal Checklist; MCQ, Marijuana Craving Questionnaire; THC-glucuronide, delta-9-tetrahydrocannabinol glucuronide; THCCOO-glucuronide, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol glucuronide; ASSR, Auditory Steady-State Response; BART, Balloon Analog Risk Task; MDMQ, Melbourne Decision Making Questionnaire; BIS, Barratt Impulsiveness Scale; ZKPQ, Zuckerman-Kuhlman Personality Questionnaire; RPQ, Risk Perception Questionnaire; CO, carbon monoxide; OLS, One Leg Stand; WAT, Walk And Turn; NS, not significant; NA, not assessed/ not applicable; >, higher/ better; <, lower/ poorer; ↓, reduction; ↑, increase; h, hour; RT, reaction time; min, minutes; RPP, Pulse rate x systolic blood pressure

Table 2. Methodological quality of human studies investigating development of tolerance in cannabis users

Study	Study design	Defined study population	Age (years)	Gender	Cannabis/ Δ9-THC concentration	Adequate exposure	Comparability of subjects	Placebo controlled	Physical and mental health comorbidity	Excluded/adjusted for tobacco, alcohol, and substance use	Statistical analyses	Funding or sponsorship
Meyer et al., 1971	✓/✕ Double-blind, counterbalanced; not randomized	✓ 1. RU, daily CBS use or nearly so; 2. NRU, CBS use ≤ 1 per week	✕	✕	✓250 mg of MJ leaf (0.9% Δ9-THC) or a self-selected known amount of MJ	✓Half h smk. at libitum from a pipe for 3 weekly sessions (420 mg by NRU, 380 mg by RU, NS)	✕	✓	✓/✕Exclusion criterion (by psychiatric interviews and psychological test); physical health not assessed	✕	✕	✓
Renault et al., 1971	✓/✕ Double blind; not randomized or counterbalanced	✓ 1. RU, current CBS use ≥ 1 per week; 2. NU, lifetime CBS use range: 0-3 times	✓ 24-45 (range)	✓Male	✓ 62.5, 125, 250, 435 mg of MJ (1.5% Δ9-THC)	✓smk. from a crucible or pipe	✕	✓	✓Exclusion criterion (by routine medical history, physical examination, blood count, urinalysis, chest x-ray, and psychiatric evaluation)	✓/✕All regular tobacco users; alcohol and other substance use not assessed	✕	✓
Cohen and Rickles, 1974	✓/✕ Double blind, randomized; not counterbalanced	✓1. RU, CBS use ≥ 4 per week; 2. NRU, CBS use at weekend (over previous year)	✕	✓Male	✓1 mg of MJ (1.4% Δ9-THC) per cig.	✓2 cig. on 2 occasions 7 days apart	✓/✕ Matched for WAIS IQ; not for other demographic characteristics	✓	✕	✕	✓ ANOVA, Duncan's Extended Range test	✓
Babor et al., 1975	✕	✓1. RU, daily CBS use; 2. NRU, CBS use > 5 per month but < daily (over previous year)	✓ 21-26 (range)	✓Male	✓~1 mg of MJ (~2.1% Δ9-THC) per cig.	✓ 21-day drug period of smk. MJ cig. on a free-choice basis	✓ Matched for demographic characteristics (age, years of education)	✕	✓Exclusion criterion (by clinical and laboratory examinations)	✓/✕ NS difference in alcohol, hallucinogens, and amphetamine use; tobacco use not assessed	✓ Pearson correlation	✓
Benowitz and Jones, 1975	✓/✕ Double blind; not randomized or counterbalanced	✓CBS use range: 2-21 cig. per week (M: 9); 1. RU, 15.2±5.3 joints per week; 2. NRU, 4.7±2.2 joints per week (M±SD)	✓ 20-27 (range), 25.1±2.2 (M±SD)	✓Male	✓1. 0 to 30 mg of Δ9-THC per caps.; 2. 20 mg of Δ9-THC per MJ cig.	✓18-20-day drug period of po. Δ9-THC maintenance (1 caps. every 4 h; up to 210 mg of Δ9-THC per day), with MJ cig. administered periodically	✕ However study participants evaluated as a whole group	✓	✓Exclusion criterion (by physical and neurological examination, screening blood and UDS, chest x-ray, ECG, and EEG)	✓Exclusion criterion for heroin, barbiturate, and amphetamine use; alcohol and tobacco use not assessed, however, subjects were asked not to use any drug for one week prior to study	✓ ANOVA, Dunnet post test	✓
Jones et al., 1976	✓/✕ Double-blind, cross-over; not randomized or counterbalanced	✓ RU, CBS use ≥ 2 per week (most with daily use)	✓ 21-31 (range), 25 (M)	✓Male	✓1. 10-30 mg of pure Δ9-THC (96%) per caps.; 2. crude extract (29% Δ9-THC, 1.5% CBN, 2.8% CBD) dissolved in 0.2-0.4 cm^3 of	✓21-42-day drug period of po. Δ9-THC or crude extract (Δ9-THC + other cannabinoids) admin. every 4h, with MJ cig. administered periodically	NA	✓	✓Exclusion criterion (by clinical and laboratory examinations); all in good physical and emotional health	✓/✕ alcohol 3-4 times per week; minimal involvement with other substances; tobacco use not assessed	✓ANOVA	✓

					95% ethanol solution; 3. 1 g of MJ (2.2% Δ9-THC) per cig.							
Nowlan and Cohen, 1977	✕	✓ 1. L+LM, 2.1 to 4.3 cig. per day; 2. HM, 6.2 cig. per day; 3. H, 8.5 cig. per day (over study period)	✓ 21-35 (range)	✓Male	✓900 mg of MJ (2.2% i.e. 19.8 mg Δ9-THC) per cig.	✓64-day drug period of smk. at least 1 MJ cig. per day with a daily ad libitum period (from 4 pm to midnight)	✕ However study participants evaluated both separated and as a whole group	✕	✓Exclusion criterion (by physical examination, laboratory tests, psychiatric interview, and MMPI)	✓/✕ Minimal involvement with other substances in at least previous 6 months; alcohol and tobacco use not assessed	✕	✓
Lindgren et al., 1981	✓/✕ Counterbalanced, cross-over; not double-blind or randomized	✓ 1. RU, daily CBS use (CBS in urine and plasma); 2. NRU, CBS use ≤ 1 per month (no CBS in urine and plasma)	✓ 19-36 (range)	✓ Male (n = 16), Female (n = 2)	✓1. 19 mg Δ9-THC (1.64%) + 0.23% CBN per MJ cig.; 2. 2 mg/ml IV Δ9-THC (5.0 mg) in 95% ethanol solution	✓2 single admin. (1 MJ cig. and 1 IV Δ9-THC injection over 2 min) at least 4 days apart	✕	✓	✓Exclusion criterion; all were in good physical and mental health, no one was on any psychoactive medication	✓No significant use of substances other than MJ; abstinent from alcohol for at least 24h prior to experiment	✕	✓
Lex et al., 1984	✓/✕ Double-blind; not randomized or counterbalanced	✓ 1. RU, CBS use ≥ 6 times per week in last 3 months, regular use for at least 2 years; 2. NRU, CBS > 2 per month but < 5 per week in last 3 months	✓ 21-36 (range), 26.1±4.35 (M±SD)	✓ Female	✓1.8% Δ9-THC) per cig.	✓1 single admin. of 1 MJ cig. (controlled inhalation: 1 puff/30 s, smoke retention: 2- 4 s).	✓ Matched for demographic characteristics (age, years of education)	✓	✓Exclusion criterion (by clinical and laboratory examinations); all in good physical and mental health	✓/✕ Matched for alcohol and substance use status; exclusion criterion for alcohol and other substance use disorders; tobacco use not assessed	✓ Correlation	✓
Mendelson et al., 1984	✓/✕ Double-blind; not randomized or counterbalanced	✓ 1. RU, daily CBS use (1-3 MJ cigarettes) for at least one year; 2. IU, weekly CBS use (1-3 MJ cigarettes) for at least one year; 3. NRU, monthly CBS use (1-3 MJ cigarettes) for at least one year	✓ 1. RU, 23-30 (range), 26.8 (M); 2. IU, 22-30 (range), 25.3 (M); 3. NRU, 22-28 (range), 24.4 (M)	✓ Male	✓1. 1 g of MJ (1.83% Δ9-THC) per cig.; 2. 2 mg of oral Nabilone; 3. 17.5 mg of Δ9-THC per caps.	✓5-day drug period of active drug admin (one dose of Nabilone, Δ9-THC, or MJ per day)	✓/✕ Age and weight reported; however differences in demographic characteristics not formally tested	✓	✓Exclusion criterion (by clinical and laboratory examinations); all in good physical and mental health	✓/✕ Exclusion criterion for alcohol and other substance use disorders; tobacco use not assessed	✓ *t*-test	✓

Marks et al., 1989	✓/✕Repeated measure; not double-blind or randomized	✓ 1. NRU, weekly CBS use (M: 3 joints per week, range: 1.5-6); 2. NU	✓ 23.4±2.6 (M±SD)	✓ Male (n = 6), Female (n = 6)	✓770 mg of MJ (1.31% Δ9-THC) + extra 70 mg and/or detoxified plant material per cig.	✓9-day drug period of smk. 1 MJ cig. per day over a 10-min period at 3 different doses (0, 2.6, and 5.2 Δ9-THC mg), alone or combined with alcohol	✓/✕ Matched for gender; not for other demographic characteristics	✓	✕	✓/✕NS difference in alcohol use (all regular users, M: 13 drink units per week); no use of other substances over the previous 24 h; tobacco use not assessed	✓ ANOVA, multiple testing correction, Duncan' test	✓
Haney et al., 1999	✓/✕Repeated measure; not double-blind or randomized	✓ RU, CBS use: 6.4±0.4 days per week (M±SD), range: 1-8 cig. per occasion	✓ 21-29 (range), 24.7±3.5 (M±SD)	✓ Male (n = 6), Female (n = 6)	✓20 or 30 mg of Δ9-THC per caps.	✓20-day drug period of po. Δ9-THC admin., 4 times/ day	✕ However study participants evaluated as a whole group	✓	✓Exclusion criterion (by medical and psychiatric evaluations)	✓/✕Most with weekly alcohol use (M: 1 day/week, two drinks per occasion); 9 tobacco users (also during experiment); other substance use infrequent (only CBS in urine on study day)	✓ ANOVA, Hunyh-Feldt correction	✓
Kirk and De Wit, 1999	✓/✕Double-blind; not randomized or counterbalanced	✓1. RU, lifetime CBS use ≥ 100 times, current use ≥ 2 per month; 2. NRU, lifetime CBS use ≤ 10 times, no use in past 4 years	✓1. RU, 27.6±5.2; 2. NRU, 25.1±3.6 (M±SD)	✓ Male (n = 12), Female (n = 9)	✓7.5 or 15 mg of Δ9-THC per caps.	✓3 evening sessions once per week	✓Matched for demographic characteristics (age, gender)	✓	✓Exclusion criterion (by DSM-IV psychiatric interview, SCL-90, ECG, and physical examination)	✓/✕Asked not to use tobacco for 6h and any substance for 24h prior to study; alcohol free on study visit; however, RU > NRU on lifetime use of other substances, tobacco and alcohol	✓ANOVA	✓
Hart et al., 2002	✓/✕ Double-blind, within-participant; not randomized or counterbalanced	✓ RU, daily CBS use (M: 12 joints per day, range: 1-35)	✓ 21-45 (range), 31.7 (M)	✓ Male (n = 10), Female (n = 2)	✓1. 1.8% Δ9-THC per MJ cig.; 2. 0-20 mg of Δ9-THC per caps.	✓18-day drug period of smk. 1 MJ cig. on 5 occasions daily and receiving 4 Δ9-THC caps.	NA	✓	✓Exclusion criterion (by medical and psychological evaluations)	✓/✕8 current alcohol users (range: 1-10 drinks per week); 7 current tobacco users (range: 2-20 cig. per day); negative UDS on study day	✓ANOVA	✓
Ponto et al., 2004	✓/✕ Randomized, cross-over; not double-blind or counterbalanced	✓1. RU, CBS use ≥ 7 times per week (M: 1.8 per day); 2. NRU, CBS use < 10 times per month (M: 1 per week)	✓ 1. RU, 20-36 (range), 21.7 (M); 2. NRU, 20-36 (range), 22.6 (M)	✓ Male (n = 18), Female (n = 18)	✓20 mg Δ9-THC per MJ cig.	✓1 single admin. of 1 MJ cig.	✓ Matched for demographic characteristics (age, gender)	✓	✕	✓/✕ Negative UDS on study day; alcohol and tobacco use not assessed	✓ ANOVA, *t*-test	✓

D'Souza et al.,2008a	✓ Double-blind, randomized, counterbalanced	✓1. RU, lifetime CBS use ≥ 100 times, last use within past week, recent use ≥ 10 per month (CBS in urine), CUD DSM-IV criteria; 2. NRU, lifetime CBS use from < 5 to > 100 times, no use in past week	✓ 18-55 (range), 25±7 (M±SD)	✕	✓ 2 ml IV Δ9-THC (0.0286 mg/kg) in 95% ethanol solution	✓1 single IV admin. of Δ9-THC over 20 min on 2 occasions at least 7 days apart	✓ Matched for demographic characteristics (age, IQ, race, weight); years of education, RU < NRU	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders + no family history of DSM Axis I disorder; and a general, physical, and neurological examination, ECG, and laboratory tests)	✓/✕ Exclusion criterion for alcohol and other substance use disorders; asked to refrain from alcohol and substances for 2 weeks prior to study (apart from RU asked to refrain from CBS only for 24h prior to study visits); tobacco use not assessed	✓ Non-parametric mixed model, Bonferroni correction	✓
D'Souza et al.,2008b	✓ Double-blind, randomized, counterbalanced	✓1. RU, lifetime CBS use > 50 times, last use ≥ 10 in past month (CBS in urine), CUD DSM-IV criteria; 2. NRU, lifetime CBS use from < 5 to > 100 times, no use in past week, use ≤ 1 in past month (no CBS in urine)	✓ 18-55 (range); 1. RU, 24.8±5.5; 2. NRU, 29±11.6 (M±SD)	✓ Male (n = 35), Female (n = 17)	✓2 ml IV Δ9-THC (2.5 or 5.0 mg) in 95% ethanol solution	✓1 single IV admin. of Δ9-THC on 2 occasions at least 7 days apart, at 2 different doses	✓ Matched for demographic characteristics (age, gender, education, socio-economic status); age and IQ used as covariates (as IQ differed between RU and NRU)	✓	✓Exclusion criterion (by DSM-IIIR or IV psychiatric interview for Axis I disorders + no family history of DSM Axis I disorder; and a general, physical, and neurological examination, ECG, and laboratory tests)	✓ Matched for smk. status; exclusion criterion for nicotine and other substance use disorders; asked to refrain from alcohol and substances for 2 weeks prior to study (apart from RU asked to refrain from CBS only for 24h prior to study visits)	✓ Non-parametric mixed model	✓
D'Souza et al.,2009	✓/✕Double-blind; not randomized or counterbalanced	✓1. RU, lifetime CBS use > 50 times, last use within past week (CBS in urine), recent use ≥ 10 in past month, CUD DSM-IV criteria; 2. NRU, lifetime CBS use from < 5 to > 100 times, no use in past week (no CBS in urine), no CUD DSM-IV criteria	✓ 18-55 (range)	✓ Male (n = 20), Female (n = 3)	✓ 2 ml IV Δ9-THC (0.0286 mg/kg) in 95% ethanol solution	✓1 single IV admin. of Δ9-THC over 20 min	✓ Matched for demographic characteristics (age, IQ, race, weight); years of education, RU < NRU; female participants only in NRU, however reanalysis excluding these subjects did not change results	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders + no family history of DSM Axis I disorder; and a general, physical, and neurological examination, ECG, and laboratory tests)	✓ Exclusion criterion for alcohol and other substance use disorders but not nicotine dependence, however only 1 current tobacco smoker (RU, ≥ 5 cig. per day); asked to refrain from alcohol and substances for 2 weeks prior to study (apart from RU asked to refrain from CBS only for 24h prior to study visits)	✓ Non-parametric/ linear mixed model, Bonferroni correction	✓
Ramaekers et al., 2009	✓Double-blind, randomized, balanced, two-way mixed model	✓1. RU, CBS use over previous year ≥ 4 per week (CBS in urine); 2. NRU, CBS use over previous year	✓ 1. RU, 23.2±3.3; 2. NRU, 22.8±2.3 (M±SD)	✓ Male (n = 17), Female (n = 7)	✓500 µg/kg Δ9-THC (13%) per MJ cig.	✓10-min of MJ smk.	✓ Matched for demographic characteristics (age, gender, weight)	✓	✓Exclusion criterion (by medical examination and laboratory analyses); no endocrine, psychiatric, and neurological	✓Exclusion criterion for substance abuse history (by questionnaires), excessive drinking (>25 standard alcoholic	✓ ANOVA, Binomial tests	✓

		≤ weekly (no CBS in urine)							condition; normal weight and BMI; no hypertension; no non-cig. smk.	consumptions per week); asked to refrain from alcohol on study day and from substances during all study (by UDS)		
Ranganathan et al., 2009	✓/✕Double-blind for both studies, randomized and counterbalanced only for 1 study	✓ 1. RU, lifetime CBS use > 50 times, last use within past week (CBS in urine), recent use ≥ 10 in past month, CUD DSM-IV criteria; 2. NRU, lifetime CBS use from < 5 to > 100 times, no use in past week (no CBS in urine), no CUD DSM-IV criteria	✓ 18-55 (range); 1. RU, 28.3±10; 2. NRU, 24.6±5 (M±SD)	✓ Male (n = 57), Female (n = 19)	✓ 2 ml IV Δ9-THC (Study I: 0.0357 or 0.0714 mg/kg; Study II: 0.0286 mg/kg) in 95% ethanol solution	✓1 single IV admin. of Δ9-THC	✓/✕ Matched for some demographic characteristics (gender, education, socioeconomic status, contraception); not for age	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders + no family history of DSM Axis I disorder; and a general, physical, and neurological examination, ECG, and laboratory tests)	✓ Exclusion criterion for alcohol and other substance use disorders but not nicotine dependence, however matched for smk. status and other substances/ alcohol use; asked to refrain from alcohol and substances for 2 weeks prior to study (apart from RU asked to refrain from CBS only for 24h before the study visits)	✓ Linear mixed model, Tukey's multiple comparison	✓
Bedi et al., 2010	✓/✕Double-blind, counterbalanced, within subject; not randomized	✓ RU, CBS use ≥ 2 per week	✓ 21-50 (range), 36.6±1.3 (M±SEM)	✓ Male	✓ 20-40 mg of Dronabinol per caps.	✓ 16-day drug period of Dronabinol caps. admin. (5 mg qid for 2 days, then 10 mg qid)	NA	✓	✓Exclusion criterion (by medical and psychiatric evaluation, ECG, and laboratory analyses)	✓/✕ Exclusion criterion for substance use disorders but not nicotine dependence	✓ ANOVA	✓
Böcker et al., 2010	✓ Double-blind, randomized, four way, cross-over	✓ CBS use, range: 2-18 cig. per month (median: 8), duration of use: 2–18 years (median: 6.5)	✓ 18-33 (range)	✓ Male	✓ 29.3, 49.2 mg, or 69.4 mg Δ9-THC per MJ cig.	✓ 4-day drug period of smk. 1 Δ9-THC cig. per day (inhalation cycle over 22 min: getting ready, 3 s; inhalation, 2 s; breath-holding, 3 s; exhalation and rest, 32 s)	✕ however age did not change results	✓	✓Exclusion criterion (by medical health questionnaire); no one was on any medication from 15 days before until the end of the study	✓ Exclusion criterion for substance use; asked to refrain from alcohol and drug intake for at least 10h prior to study (by staying in hospital overnight and UDS); alcohol and tobacco use did not change results	✓ MANOVA	✓
Barkus et al., 2011	✓ Double-blind, randomized, counterbalanced, repeated measures	✓ lifetime CBS use: 153±324 times (M±SD), range: 1-1000; last use: 43 weeks ago, range: 2-288	✓ 26.3±4.2 (M±SD)	✓ Male	✓ 5 ml IV Δ9-THC (2.5 mg) in 2.5% ethanol solution	✓1 single IV admin. of Δ9-THC, 1ml/min	NA	✓	✓Exclusion criterion (by General Health Questionnaire); no mental illness + no family history of mental illness, no ongoing or serious past physical illness	✓/✕ Exclusion criterion for substance use disorders but not nicotine dependence (by MAST and DAST); asked to refrain from alcohol and drugs for 24h prior to study (by UDS)	✓ Friedman's test, Wilcoxon's test, Spearman's correlation	✓

Bosker et al., 2012	✓ Double-blind, randomized, balanced, three way, cross-over	✓ 1. RU, daily CBS use or nearly so (range: 7.7-23.1 joints per week), lifetime CBS use: 2442.2±708.8 times (M±SD), pattern of use > 160 times per year (CBS in urine); 2. NRU, lifetime CBS use: 274.1±89.6 times (M±SD), pattern of use range: 5-36 times per year (no CBS in urine)	✓ 23.6±0.6 (M±SD)	✓ Male (n = 14), Female (n = 10)	✓ 10-20 mg of Dronabinol per caps.	✓2 single admin. of dronabinol caps., at least 4 days apart	✓/✕ Matched for gender; not for other demographic characteristics	✓	✓Exclusion criterion; all free from psychotropic medication and in good physical health, no major medical condition, cardiovascular abnormalities, hypertension, or past/ current psychiatric disorder	✓/✕ Exclusion criterion for substance abuse or addiction to non-cannabinoids and excessive drinking; asked to refrain from alcohol and caffeine for 24h prior to study (by ABT and UDS); tobacco used not assessed	✓ ANOVA, Chi-Square, Spearman's correlation	✓
D'Souza et al.,2012	✓ Double-blind, randomized, counterbalanced, cross-over	✓/✕ lifetime CBS use from < 10 to > 1000 times, last use: 415.02 days ago (range: 1-3650), recent use range: 0-29 days in past month, pattern of use from 1 per year to 7 per week; 1. RECU, CBS use in last 30 days; 2. NRECU, no CBS use in last 30 days	✓ 18-35 (range), 25.9±7.8 (M±SD)	✓ Male (n = 17), Female (n = 9)	✓ IV Δ9-THC (0.015 or 0.03 mg/kg) in ethanol solution	✓1 single IV admin. of Δ9-THC on 2 occasions, at 2 different doses, and over 10 min, at least 3 days apart	✕	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders + no family history of DSM Axis I disorder; and a general, physical, and neurological examination, ECG, and laboratory tests)	✓ Exclusion criterion for substance use disorders but not nicotine dependence, however, tobacco use ≤ 10 per day, asked to refrain from alcohol, caffeine, and substances for 2 weeks prior to study, apart from RU asked to refrain from CBS only for 24h prior to study visits (by UDS)	✓ ANOVA, *t*-test, non-parametric mixed model	✓
Theunissen et al., 2012	✓ Double-blind, randomized, balanced, two way, cross-over	✓1. RU, CBS use > 4 times per week, pattern of use: 340±86 (M±SD) per year (CBS in urine); 2. NRU, CBS use < 2 times per week, pattern of use: 55±36 (M±SD) per year (no CBS in urine)	✓ 1. RU, 23.2±3.3; 2. NRU, 22.8±2.3 (M±SD)	✓ Male (n = 17), Female (n = 7)	✓500 µg/kg Δ9-THC (13%) per MJ cig. (0.8 g)	✓10-15-min of MJ smk. (RU, 0.256 g; NRU, 0.277 g)	✓ Matched for demographic characteristics (age, gender, and weight)	✓	✓Exclusion criterion (by medical screening and laboratory tests); all free from psychotropic medication and in good physical health; no major medical, endocrine, and neurological condition, hypertension, color blindness, dyslexia, or past/ current psychiatric	✓Exclusion criterion for substance abuse or addiction to non-cannabinoids, excessive drinking (> 20 consumptions per week), excessive smk. (> 25 cig. per day); asked to refrain from alcohol for 24h prior to study, caffeine on study day, and substances	✓ ANOVA, Pearson correlation	✓

									disorder	during all study (except CBS, only NRU asked to refrain for at least 5 days prior to study) (by ABT and UDS)		
Fabritius et al., 2013	✓/✕ Cross-over; not double-blind, counterbalanced or randomized	✓1. RU, CBS use ≥ 10 joints per month (2.3 joint per week) in last 3 months (CBS in urine); 2. NRU, CBS use ≥ 1 joint per month but ≤ 1 joint per week in last 3 months	✓ 18-30 (range); 1. RU, 22.7+2.4 (M+SD); 2. NRU, 23.9+3 (M+SD)	✓ Male	✓11% Δ9-THC and < 1% CBD per MJ cig.	✓1 single admin. of 1 MJ cig. (inhalation cycle: getting ready and start signal, 3 s; inhalation, 2 s; breath-holding, 5 s; exhalation and rest, 50 s. Sequence repeated until 2/3 of the joint was consumed)	✓ Matched for demographic characteristics (age and ethnicity)	✓	✓Exclusion criterion (by structured interview conducted by a medical staff)	✓/✕Exclusion criterion for substance use; alcohol and tobacco use not assessed	✓ Mann–Whitney U test	✓
Gorelick et al., 2013	✕	✓RU, lifetime CBS use > 1000 times, daily pattern of use in past 3 months (5.5±5.9 joints per day, M±SD; range: 1-24), last use within 24 h (CBS in urine)	✓ 18-45 (range), 24.6+3.7 (M±SD)	✓ Male	✓ 20 mg of Dronabinol per caps.	✓ 6-day drug period of Dronabinol caps. admin. every 3.5-6 h (day 1: 40 mg, day 2-4: 100 mg; day 5-6: 150 mg)	NA	✕	✓Exclusion criterion; no past/ present significant medical disease, no history of psychosis, no current DSM-IV Axis I disorder, normal cardiac function, IQ > 85, no previous adverse events related to CBS	✓/✕Exclusion criterion for substance use disorders (by UDS) but not nicotine or caffeine dependence, ≥ 6 alcohol drinks/day ≥4 times/week in the month before study; 9 daily tobacco users (17.9±18.8 cig. per day), others past users	✓ ANOVA, Greenhouse -Geisser correction	✓
Sewell et al., 2013	✓ Double-blind, randomized, counterbalanced	✓/✕ 1. RECU, CBS ≥ 8 times in last 30 days; 2. NRECU, CBS ≤ 2 per week in last 30 days	✓ 18-35 (range); 1. RECU, 20.7+1.4 (M+SD); 2. NRECU, 23.1+3.6	✓ Male (n = 33), Female (n = 11)	✓ IV Δ9-THC (0.015 to 0.05 mg/kg) in ethanol solution	✓1 or 2 single IV admin. of Δ9-THC, at 3 different dose ranges, and at least 3 days apart	✓/✕ Matched for some demographic characteristics (gender, education, ethnicity, BMI, IQ, handedness); not for age (RECU < NRECU)	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders and a general, physical, and neurological examination, ECG, and laboratory tests)	✓ Exclusion criterion for substance use disorders, asked to refrain from alcohol and substances for at least 1 week prior to study (for NRU by UDS), and matched for smk. status	✓ ANOVA, *t*-test, Chi-Square/ Fisher's test, Cohen's *d*, linear mixed model	✓
Vandrey et al., 2013	✓/✕ Counterbalanced, within-subjects, cross-over; not randomized	✓RU, pattern of CBS use: 25 days per month in past 3 months, 4+2 times (M±SD) per day (CBS in	✓ 18-55 (range), 34+9 (M±SD)	✓ Male (n = 12), Female (n = 1)	✓ 10, 20, 40 mg of Dronabinol per caps.	✓ 51-day drug period of Dronabinol caps. admin. (10, 20,or 40 mg tid) followed by a single CBS	NA	✓	✓Exclusion criterion (by DSM-IV-TR psychiatric interview for Axis I disorder and ECG); all free from psychotropic	✓/✕ Exclusion criterion for substance use disorders but not nicotine dependence; no acute drug or alcohol intoxication	✓ Regression, Student-Newman-Kuels multiple	✓

		urine), 11 subjects with CBS dependence				exposure (5.7% Δ9-THC, 0.8 g, 5 puffs)			medication; no history of seizures, severe hepatic impairment, or conditions associated with cognitive impairment	apart from CBS (by ABT and UDS)	comparison test, correlation	
Cortes-Briones et al., 2015	✓ Double-blind, randomized, counterbalanced, cross-over	✓/✕ lifetime CBS use from ≤ 5 to > 1000 days, last use: 402.72 days ago (range: 1-3650), recent use range: 1-29 days in past month, pattern of use from 1 per year to 7 per week; 1. RECU, CBS use in last 30 days; 2. NRECU, no CBS use in last 30 days	✓ 18-35 (range), 25.7±7.6 (M±SD)	✓ Male (n = 14), Female (n = 6)	✓ IV Δ9-THC (0.015 or 0.03 mg/kg) in ethanol solution	✓1 single IV admin. of Δ9-THC on 2 occasions, at 2 different doses, and over 10 min, at least 3 days apart	✕	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders + no family history of DSM Axis I disorder; and a general, physical, and neurological examination, ECG, and laboratory tests)	✓ Exclusion criterion for substance use disorders but not nicotine dependence, however, tobacco use ≤ 10 per day; asked to refrain from alcohol, caffeine, and substances for 2 weeks prior to study, apart from RU asked to refrain from CBS only for 24h prior to study visits (by UDS)	✓ Generalized estimating equations, Holm–Bonferroni sequential procedure	✓
Desrosiers et al., 2015	✕	✓1. RU, CBS use ≥ 4 times per week in past 3 months (CBS in urine); 2. NRU, CBS use < 2 times per week in past 3 months	✓ 18-45 (range); 1. RU, 25.7±4.6; 2. NRU, 31.4±6.3 (M±SD)	✓ Male (n = 18), Female (n = 7)	✓54 mg Δ9-THC (6.8±0.2%) per MJ cig.	✓10-min of MJ smk.	✓/✕ Matched for some demographic characteristics (gender, BMI); not for age and race/ ethnicity	✕	✓/✕ Exclusion criterion; no medical condition, history of neurological illness, hypertension, tachycardia; psychiatric comorbidity not assessed	✕	✓ ANOVA, *t*-test, Hunyh-Feldt correction	✓
Farris et al., 2016	✓/✕Double-blind, counterbalanced, within-subjects; not randomized	✓ CBS use ≥ 2 days per week in past month, and ≥ weekly in past 6 months (2.1±1.2 times per day, M±SD); CBS dependence: 13.6%, CBS abuse: 29.5%; 1. RU, CBS use on 94.4% of days (~ 6.6 days per week); 2. NRU, CBS use on 50.0% of days	✓ 18-44 (range), 21.5±4.5 (M±SD)	✓ Male (n = 58), Female (n = 30)	✓ 2.8-3.0% Δ9-THC per MJ cig.	✓smk. 1 MJ cig.	✕	✓	✓Exclusion criterion (by DSM psychiatric interview for Axis I disorders and physical exam for contraindicated medical issues); no BMI > 30	✓ Exclusion criterion for substance use (by UDS) and tobacco use ≥ 20 cig. per day (46.6% smokers, 4.2±3.8 cig. per day on smk. days); 29.5 % alcohol users (4.2±2.4 drinks per drinking day); asked to refrain from alcohol for 24h, caffeine for 1h, and CBS and tobacco for 15h prior to study (by ACMT and ABT)	✓*t*-test, refression	✓

Ramaekers et al., 2016	✓ Double-blind, randomized, counterbalanced, three way, cross-over	✓ CBS use ≥ 2 times in past 3 months, recent use: 44.8 times in past 3 months (range: 2-100; clustered in 1. L use, 1-24 times; 2. LM use, 25-49 times; HM use, 50-74 times; H use, 75-100 times)	✓ 18-39 (range), 22.8 (M)	✓ Male (n = 96), Female (n = 26) out of original cohort of 132	✓300 µg/kg Δ9-THC (11-12%) vaporized CBS	✓ vap. dose over 2-3 min	✕ However study participants evaluated as a whole group	✓	✓Exclusion criterion (by medical examination, laboratory analyses, and ECG); all free from psychotropic medication and in good physical and mental health, normal weight (BMI, 18-28), no cardiovascular abnormalities, hypertension, or past/ current psychiatric or neurological disorder	✓/✕ Exclusion criterion for cocaine dependence, excessive alcohol use (> 20 units per week) or smk. (> 15 cig. per day); use of MDMA (88%), amphetamines (73%), mushrooms (61%), LSD (20%), and other drugs (60%, nitrous oxide, DMT, and ketamine); asked to refrain from drug and alcohol use (by ABT and UDS)	✓ ANOVA, Pearson correlation	✓
Newmeyer et al., 2017a	✓ Double-blind, randomized, double-dummy, cross-over	✓1. RU, CBS use ≥ 5 times per week in past 3 months (CBS in urine); 2. NRU, CBS use ≥ 2 times per month but < 3 times per week in past 3 months (no CBS in urine)	✓ 18-46 (range)	✓ Male (n = 15), Female (n = 5)	✓1. 0.734±0.05 g Δ9-THC (6.9±0.95%) per MJ cig.; 2. CBS-containing brownie; 3. Vaporized CBS	✓po., smk., or vap. dose ad libitum over 10 min	✓/✕ Matched for some demographic characteristics (age, gender, BMI); not for race/ ethnicity	✓	✓Exclusion criterion (by medical and psychological evaluation)	✕, tobacco use allowed while on the research unit	✓ *t*-test, ANOVA, planned Helmert contrasts, Bonferroni correction	✓
Newmeyer et al., 2017b	✓ Double-blind, randomized, double-dummy, cross-over	✓1. RU, CBS use ≥ 5 times per week in past 3 months (CBS in urine); 2. NRU, CBS use ≥ 2 times per month but < 3 times per week in past 3 months (no CBS in urine)	✓ 18-46 (range)	✓ Male (n = 15), Female (n = 5)	✓1. 0.734±0.05 g Δ9-THC (6.9±0.95%) per MJ cig.; 2. CBS-containing brownie; 3. Vaporized CBS	✓po., smk., or vap. dose ad libitum over 10 min	✓/✕ Matched for some demographic characteristics (age, gender, BMI); not for race/ ethnicity	✓	✓Exclusion criterion (by medical and psychological evaluation)	✓/✕ Exclusion criterion for substance, caffeine, or nicotine dependence	✓ *t*-test, ANOVA, Greenhouse –Geisser correction	✓

RU, regular users; CBS, CBS; NRU, non-regular users; IU, intermittent users; M, mean; SD, standard deviation; L, light; LM, low moderate; HM, high moderate; H, heavy; NU, non-users; CUD, CBS use disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; RECU, recent users; NRECU non recent users; mg, milligrams; Δ9-THC, Delta-9-tetrahydrocannabinol; MJ, marijuana; CBN, cannabinol; CBD, Cannabidiol; ml, milliliter; IV, intravenous; kg, kilogram; µg, micrograms; g, grams; h, hour; smoking, smk.; NS, not significant; cigarette(s), cig.; capsule(s), caps.(s); po., per os; min, minute(s); administration(s), admin.; qid, four times per day; tid, three times per day; vap., vaporized; WAIS, Wechsler Adult Intelligence Scale; IQ, Intelligence quotient; NA, not applicable; UDS, urine drug screen; ECG, electrocardiogram; EEG, electroencephalogram; MMPI, Minnesota Multiphasic Personality Inventories; SCL-90, Symptom Checklist-90; BMI, body mass index; MAST, Michigan Alcohol Screening Test; DAST, Drug Abuse Screening Test; ABT, Alcohol Breath Test; ACMT, Alveolar Carbon Monoxide Test; MDMA, 3,4-Methylenedioxymethamphetamine; LSD, Lysergic acid diethylamide; DMT, N,N-Dimethyltryptamine; ANOVA, analysis of variance; MANOVA, multivariate analysis of variance

Table 3. Summary of the effects of cannabis on development of tolerance in man

Domain	Number of subjects per study (M ± SD)	Total number of subjects (n)	Evidence
Intoxication and subjective effects	28.6 ± 24.5	629	15 +; 7 -
Cardiac parameters			
Increase in heart rate	23.5 ± 13.3	376	11 +; 5 -
Hypotension	26.1 ± 14.3	183	3 +; 4 -
Cognition			
Memory and learning	23.6 ± 14.2	189	6 +; 2 -
Attention	30 ± 33	330	7 +; 4 -
Psychomotor ability	31.6 ± 34.3	316	6 +; 4 -
Impulsivity	57 ± 56.3	171	3 –
Time perception		44	+
Psychopathological symptoms			
Psychotomimetic symptoms	27.5 ± 17.9	110	4 +
Perceptual alterations	33.7 ± 15.9	101	3 +
Mood changes	24 ± 25.2	72	1+; 2 -
Anxiety	38.5 ± 19.1	77	2 +
Confusion	33.5 ± 20.6	67	2 +
Cannabinoid levels	39.4 ± 32.1	473	8 +; 4 -
EEG signals	29.2 ± 13.5	146	5 +
Other behavioral measures			
Driving skills	22 ± 2.8	44	2 +
Sleep quality	24 ± 25.2	72	2 +; 1 -
Weight	30 ± 32.5	60	2 -

Food-related behavior Social behavior	10.3 ± 2.9 9.5 ± 3.5	31 19	1 +; 2 - 2 -
Other physiological measures			
Cortisol	64 ± 17	128	2 +
Prolactin	44.75 ± 24.3	179	3 +; 1 -
BDNF		23	+
Dopamine release		9	-
Breath holding		88	+
Respiration rate/ CO		20	-
Other body response		53	+

EEG, electroencephalogram; BDNF, brain-derived neurotrophic factor; CO, carbon monoxide; '+' refers to positive evidence of tolerance; '-' refers to negative evidence of tolerance